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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.hhs.gov.**

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Structured Abstract

Objectives: This is a systematic review of evidence on issues in managing small cell lung cancer (SCLC). Key questions addressed are: the sequence, timing and dosing characteristics of primary thoracic radiotherapy (TRTx) for limited-stage disease; primary TRTx for extensive-stage disease; effect of prophylactic cranial irradiation (PCI); positron emission tomography (PET) for staging; treatment of mixed histology tumors; surgery; and second- and subsequent-line treatment for relapsed/progressive disease.

Data Sources: MEDLINE®, EMBASE, and the Cochrane Register

Review Methods: The review methods were defined prospectively in a written protocol. We sought randomized controlled trials that compared the interventions of interest. Where randomized trials were limited or nonexistent, we sought additional studies. We performed meta-analysis of studies that compared early and late TRTx.

Results: The strongest evidence available for this Report is a patient-level meta-analysis showing that PCI improves survival of SCLC patients who achieved complete response following primary therapy from 15.3 percent to 20.7 percent ($p=0.01$). No other question yielded evidence so robust. The case for concurrent over sequential radiation delivery rests largely on a single multicenter trial. Support for early concurrent therapy comes from one multicenter trial, but two other multicenter trials found no advantage. Our meta-analysis did not find significant reductions in 2- and 3-year mortality for early TRTx. Favorable results from a single-center trial on TRTx for extensive stage disease need replication in a multicenter setting. For other questions (i.e., management of mixed histology disease; surgery for early limited SCLC), relevant comparative studies were nonexistent. PET may be more sensitive in detecting disease outside the brain than conventional staging modalities, but studies were of poor quality and reliable estimates of performance are not possible.

Conclusions: PCI improves survival among those with a complete response to primary therapy. A research agenda is needed to optimize the effectiveness of TRTx and its components. PET for staging may be useful, but its role awaits clarification by rigorous studies. No relevant evidence was available to address management of mixed histology disease or surgery for early limited SCLC.

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Appendixes and Evidence Tables for this report are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

Executive Summary

Introduction

Small-cell lung cancer (SCLC) accounts for 13–20 percent of the 172,570 new cases and 163,510 deaths from lung cancer expected in the U.S. in 2005 (American Cancer Society, 2005; Murren, Glatstein, and Pass, 2001; Simon and Wagner, 2003; Physicians Data Query 2005; Chua, Steer, and Yip, 2004; Ettinger, 2004; Stupp, Monnerat, Turrisi, et al., 2004). Untreated SCLC is aggressive, with a median survival of 2 to 4 months after diagnosis (Physicians Data Query, 2005).

The American College of Chest Physicians (ACCP), nominated SCLC as a topic for an evidence report to support updating of its 2003 guideline. Consultation with technical experts, some nominated by ACCP, identified nine key issues in need of systematic review:

1. For limited-stage SCLC, what are the relative benefits and harms (survival, toxicity, and quality of life) of thoracic radiotherapy (TRTx) combined with chemotherapy either in alternating fashion, concurrently or sequentially?

2. For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is given in early versus late chemotherapy cycles?

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

    - accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens (<10 Gy per week) versus split courses delivered over the standard interval; and

    - single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation (PCI)?

6. Does the addition of positron emission tomography (PET) scanning improve the accuracy of staging for patients diagnosed with SCLC, over the use of other techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), without PET?

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Methods

The review methods were defined prospectively in a written protocol. A technical expert group provided consultation. The draft report was also reviewed by other experts and stakeholders.

Primary outcomes include: duration of survival, disease- or progression-free survival; quality of life; brain metastasis; and adverse events. Secondary outcomes include: response rates; response duration; and recurrence. For key question 6 (PET staging) additional outcomes are diagnostic accuracy and changes in patient management.

Electronic database searches of MEDLINE (through 12/21/04), EMBASE (through 3/04/05), and the Cochrane Controlled Trials Register (through 3/11/05).were conducted. The search was not limited to English language, but foreign-language references without abstracts were excluded. Relevant conference proceedings were searched electronically.

We sought randomized, controlled trials (RCTs) that compared the interventions of interest. Where randomized trials were limited or nonexistent, we sought additional studies. For question 8 (surgery), we also sought nonrandomized comparative trials, prospective or retrospective. For question 9 (second- or subsequent line therapy), we also sought phase II multicenter studies reporting on at least 25 patients. For question 6 (PET staging), we sought single-arm trials that permitted computation of specificity and sensitivity in relation to an appropriate reference standard.

A single reviewer screened titles and abstracts for full-text retrieval; citations marked as uncertain were reviewed by a second reviewer. Review of full-text articles was conducted in the same fashion to determine inclusion in the systematic review. One reviewer performed primary data abstraction and a second reviewer reviewed the evidence tables for accuracy. All disagreements were resolved by consensus.

The general approach to assessing quality of evidence from studies of therapeutic interventions developed by the U.S. Preventive Services Task Force (Harris, Helfand, Woolf, et al., 2001) was applied. For diagnostic studies, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

We performed meta-analysis that combined studies included in key questions 1 and 2. The metrics were 2-year and 3-year mortality relative risks (RRs). Publication bias was tested using Egger's linear regression (Egger, Davey Smith, Schneider, et al., 1997). A standard test for heterogeneity, the Q statistic, was used (Cochran, 1954). If significant, the combined RR point

estimate was computed with a random effects (RE) model (DerSimonian and Laird, 1986). If not, a fixed effects (FE) model would be used (Cochran, 1937). Pooled estimates of treatment effects were derived using the inverse variance-weighted method (Cochran, 1937). Subgroup/sensitivity analyses were performed for earliest initiation of TRTx, hyperfractionation; platinum chemotherapy; concurrent TRTx; and study quality. Analyses were performed using STATA 9.0 and Microsoft Excel 2002.

Results

1. For limited-stage SCLC, what are the relative benefits and harms of TRTx combined with chemotherapy either in alternating fashion, concurrently, or sequentially?

One multicenter trial and one single-center trial (n=307) compared concurrent and sequential TRTx. Results are not conclusive but suggest better outcomes for concurrent TRTx. Overall survival adjusted for confounders significantly favored concurrent TRTx in the Takada, Fukuoka, Kawahara, et al. trial (2002; n=228), although unadjusted results were not significant. Additionally, the Park, Kim, Jeong, et al. (1996) trial found significantly longer response duration for concurrent TRTx. Of 11 types of adverse events reported, only leukopenia occurred significantly more frequently in the concurrent TRTx group in both studies.

No conclusions could be drawn on alternating TRTx. No significant differences in overall or progression-free survival were found in any of four trials: two (n=458) comparisons to sequential TRTx; one (n=156) comparison concurrent TRTx; and one (n=199) comparison of early and late alternating TRTx.

2. For limited-stage SCLC, do outcomes differ if concurrent TRTx is given in early versus late chemotherapy cycles?

The evidence is equivocal, finding no difference or small advantage for early concurrent TRTx. One large multicenter trial of good quality significantly favored concurrent therapy given in an early cycle (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988), as did 2 smaller trials. Of the two large multicenter trials that found no significant difference in survival, one did not use platinum chemotherapy (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988) and the other is published only in abstract (James, Spiro, O'Donnell, et al., 2003). Leukopenia/neutropenia appeared to be more common with early TRTx.

Meta-analysis was performed in an attempt to obtain clearer results. Studies selected for Key Questions 1 and 2 were viewed as comparing early and late TRTx, and were pooled to give a more robust analysis. We did not find statistically significant reductions in 2- and 3-year mortality for early TRTx over late TRTx. The relative risk (RR) at 2 years was 0.921 (95 percent CI: 0.844–1.005) and the RR at 3 years was 0.991 (95 percent CI: 0.955–1.029).

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx?

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited. Two RCTs compared one versus two fractions a day for previously untreated SCLC. One compared an accelerated regimen versus the standard duration, while the other compared a split-course regimen versus the standard duration.

Compared to a single daily fraction, two daily fractions delivered concurrently with platinum chemotherapy improved overall survival (23 vs. 19 months, log rank p=0.04) in a large multicenter trial of good quality (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000; n=417). The second trial is difficult to interpret, since multiple variables were studied simultaneously (Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999; n=161), but there was no difference in survival with one versus two fractions per day.

Esophagitis was more frequent with two fractions daily.

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding thoracic radiation therapy to chemotherapy for primary treatment of extensive-stage SCLC?

One single-center RCT (Jeremic, Shibamoto, Nikolic, et al., 1999; n=99) suggests that adding concurrent TRTx improves survival of patients with extensive-stage disease that responds to an initial three cycles of platinum/etoposide chemotherapy with a complete response (CR) outside the thorax and at least a partial response in the thorax. Uncontrolled data from the same trial suggest little to no benefit for other patients. Grades 3/4 esophagitis were more common with TRTx.

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation?

An individual patient data meta-analysis on seven RCTs (N=987) conducted by the Cochrane PCI Overview Collaborative Group shows that PCI improves survival of SCLC patients in CR after primary therapy. PCI increases 3-year survival from 15.3 percent to 20.7 percent (p=0.01), an absolute increase of 5.4 percent. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial reported after the meta-analysis generally agrees with these findings.

Subgroup analyses showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage or performance status at diagnosis, and whether or not TRTx is part of the induction regimen. Survival benefit does not appear to differ among subgroups.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving complete response may reduce the likelihood of brain metastases. However, these hypotheses, derived from subgroup analyses, require formal testing in RCTs.

Although data are scant, acute toxicities of PCI seem tolerable at the doses used in these

trials (8–40 Gy in 1.8 to 3 Gy fractions) and neurocognitive deficits no greater than existed prior to PCI.

6. Does the addition of PET scanning improve the accuracy of staging for patients with SCLC over the use of other techniques, including CT and MRI, without PET?

The evidence is limited and of poor quality, thus no conclusions can be drawn. Six studies (N=277) suggest that, except for brain metastases, PET added to conventional staging is more sensitive in detecting disease. However, there is so much uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. The frequency of incorrect changes in stage attributable to PET is unknown due to incomplete reporting.

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

There are few studies of any design that included patients with mixed histology. No conclusions can be drawn from the available evidence.

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

We sought studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials and 8 nonrandomized comparative studies were reviewed. None studied a homogeneous group of patients with respect to nodal status; nor were separate outcomes reported for a subgroup of patients without evidence of nodal involvement. Thus no conclusion can be drawn.

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC?

Nine RCTs address second- or subsequent-line treatment of SCLC, each of which compared different sets of chemotherapy regimens. Two randomized trials directly compared chemotherapy with best supportive care for recurrent SCLC. The first studied second-line methotrexate plus doxorubicin and found an overall response rate of 23 percent for the chemotherapy arm. The second reported that oral topotecan resulted in a statistically significant increase in survival (26 weeks vs. 14 weeks) and slower decline in quality of life. High-grade neutropenia occurred in one-third of patients. Another trial compared oral versus intravenous topotecan; leukopenia and neutropenia were more frequent with the intravenous route, but survival and response were no greater. Other RCTs found higher rates of adverse events for one treatment over another, but no associated survival advantage that would offset increased high grade toxicity.

Five multicenter phase II trials of note published since 2000 have reported overall response rates of 20 percent or more. Only one study, using topotecan plus cisplatin, enrolled more than 50 patients. Approximately one-fourth of both sensitive and refractory patients responded.

Three-quarters or more of both patient groups had high-grade leukopenia and neutropenia. A small study of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide, and cisplatin achieved a high overall response rate and high-grade leukopenia in nearly all patients. One-quarter of those given paclitaxel plus carboplatin had a response and about half had high-grade neutropenia. In a study of doxorubicin plus carboplatin, nearly half of patients responded; however, 4 out of 5 had grade 3 or 4 granulocytopenia.

Discussion and Future Research

The strongest evidence available for this report is a patient-level meta-analysis showing that PCI improves survival of SCLC patients who achieved CR following primary therapy. No other question yielded evidence so robust. Our conclusions typically relied on a single trial showing treatment effects that were modest at best, and sometimes equivocal. This was apparent in our review of evidence for the sequence, timing, dosing and fractionation of TRTx. For example, the case for concurrent over sequential delivery rests largely on a single multicenter trial (Takada, Fukuoka, Kawahara, et al., 2002). Support for early concurrent therapy comes from the multicenter trial by Murray-Coy-Field (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988); however, two other multicenter trials, (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988; James, Spiro, O'Donnell, et al., 2003 [abstract]) found no advantage. However, the meta-analysis of 11 studies did not find significant reductions in 2- and 3-year mortality for early TRTx. For some questions (i.e., management of mixed histology disease; surgery for early limited SCLC) comparative trials were nonexistent.

Results reported by Jeremic, Shibamoto, Nikolic, et al., (1999) on TRTx for extensive-stage disease, need replication in a multicenter setting.

PET may be more sensitive in detecting disease outside the brain than conventional staging modalities. Future studies should fully report the frequency of correct and incorrect staging changes when PET is added to conventional tests and should link diagnostic performance to outcomes such as improvement in survival or reduced morbidity. Studies should be conducted according to standards described by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and reported according to the Standards for Reporting of Diagnostic Accuracy (STARD) statement.

Complicating the evaluation of SCLC treatment are overall poor outcomes and small effect sizes, necessitating large numbers of patients in trials. Furthermore, interventions are multimodal with a multiplicity of variables that might contribute to the effectiveness.

Trials that are poorly designed, conducted, or reported waste limited resources. To advance clinical knowledge and practice, the field should adhere to standards of research quality and set an agenda for research priorities. Given modest gains in survival, quality of life assessment should be integral to clinical trials and should adhere to recommended research methods, including handling of missing data.

Conclusions

PCI improves survival among those with a complete response to primary therapy. A research agenda is needed to optimize the effectiveness of TRTx and its components. PET for staging may be useful, but its role awaits clarification by rigorous studies. No relevant evidence was available to address management of mixed histology disease or surgery for early limited SCLC.

Chapter 1. Introduction

This systematic review summarizes and analyzes evidence on selected aspects of managing patients diagnosed with small cell lung cancer (SCLC). This section outlines the review's clinical scope, highlights relevant aspects of the disease's epidemiology and public health impact, describes briefly current treatment guidelines and uncertainties, and overviews key questions to be addressed.

Objective of Systematic Review

The American College of Chest Physicians (ACCP) is preparing to update its 2003 evidence-based guideline on diagnosis and management of lung cancer. To support this effort, the ACCP nominated SCLC as a topic for systematic review by one of the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPC). Consultation with technical experts, some nominated by ACCP, identified key issues in need of systematic review.

Epidemiology and Public Health Impact of Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for 13–20 percent of the estimated 172,570 new cases and 163,510 deaths from lung cancer expected in the U.S. in 2005 (American Cancer Society, 2005; Murren, Glatstein, and Pass 2001; Simon and Wagner, 2003; Physicians Data Query 2005; Chua, Steer, and Yip, 2004; Ettinger 2004; Stupp, Monnerat, Turrisi, et al., 2004). Untreated SCLC has the most aggressive clinical course of any lung tumor, with a median survival of only 2 to 4 months after diagnosis (Physicians Data Query, 2005). Since it metastasizes rapidly, SCLC is present outside the hemithorax of origin in most patients at diagnosis (Physicians Data Query, 2005).

Current Staging and Treatment Strategies for Small Cell Lung Cancer

Staging and Classification

SCLC is also known as "oat cell" carcinoma or small cell undifferentiated carcinoma (American Cancer Society, 2004). SCLC can be subtyped according to cellular classification as 1) small cell carcinoma; 2) mixed small cell/large cell carcinoma; or 3) combined small cell

carcinoma (i.e., small cell lung cancer combined with neoplastic squamous and/or glandular components) (Physician Data Query, 2005).

Although the TNM classification scheme used for non-SCLC is applicable to SCLC staging (Cameron and Schwartz, 2005), most clinicians use a simplified two-stage scheme developed by the Veterans Administration Lung Cancer Study Group (Simon and Wagner, 2003; Physician Data Query, 2005). Limited-stage SCLC (approximately 30 percent of patients at diagnosis) includes those with tumor confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes (Simon and Wagner, 2003; Physicians Data Query, 2005). In extensive-stage SCLC, tumor has spread outside these limits; patients with distant metastases are always considered to have extensive disease (Physician Data Query, 2005). At the time of diagnosis, 60–65 percent of SCLC patients have extensive disease (Osterlind, 2001). Estimates of median survival with current therapies are 16–24 months for those with limited-stage disease, and 6–12 months for those with extensive-stage disease (Physician Data Query, 2005).

Diagnostic procedures commonly used to establish the presence of distant metastases include bone marrow aspiration, brain scans using computed tomography (CT) or magnetic resonance imaging, chest and abdomen scans using CT, and radionuclide bone scans (Physician Data Query, 2005; Murren, Turrisi, and Pass, 2005). Whether positron emission tomography (PET) metabolic scanning using 18-fluorodeoxyglucose (18-FDG) provides any additional information to current staging techniques is uncertain (Murren, Turrisi, and Pass, 2005; Simon and Wagner, 2003).

Treatment Strategies

Treatments for SCLC are selected by stage and other features of disease extent (Physician Data Query, 2005). Few patients with extensive SCLC currently attain long-term survival. Their survival at 2 years after diagnosis is approximately 5 percent and at 5 years is less than 1 percent (Murren, Turrisi, and Pass, 2005).

Over time, there has been better success in the management of patients with limited disease. The proportion of long-term survivors among these patients has doubled from the 1970s to the 1990s (Janne, Freidlin, Saxman, et al., 2002; Murren, Turrisi, and Pass, 2005). While this may be due in part to stage migration, it is probably more associated with the change in practice of using platinum-based, rather than cyclophosphamide-based, combination chemotherapy regimens (Murren, Turrisi, and Pass, 2005). Attempts to improve on those results, either by adding a third drug or by substituting newer drugs have not yielded more long-term survivors thus far. It appears that further improvement requires both more and more complete responses to primary therapy (i.e., chemotherapy and radiation). Absent that, other interventions seem to largely alter the pattern of relapse, but not overall survival.

Chemotherapy. Chemotherapy is used for most patients, either as adjuvant therapy for the few patients eligible for surgery, or as primary therapy for patients with inoperable tumors. Preferred regimens have evolved over time (Murren, Turrisi, and Pass, 2005). Current guidelines recommend platinum-etoposide combinations in patients with limited-stage disease and platinum-based regimens in patients with extensive-stage disease (Simon and Wagner, 2003; Osterlind, 2001). According to the 2003 ACCP guidelines, there is no evidence on the benefit of maintenance chemotherapy in any patient achieving a partial or complete remission, and maintenance therapy is not recommended outside of a clinical trial (Simon and Wagner, 2003).

Surgery. Surgery is usually limited to patients with smaller tumors (T1 or T2) and no evidence of nodal involvement or spread outside the hemithorax of origin (Physician Data Query, 2005). Whether surgery added to chemotherapy for patients with limited-stage disease improves survival is currently uncertain.

Thoracic Radiotherapy. Meta-analyses published in the 1990s demonstrated the benefit of adding thoracic radiotherapy (TRTx) to chemotherapy in patients with limited-stage disease (Warde and Pignon, 1992; Pignon, Arrigada, Ihde, et al., 1992). Addition of TRTx to chemotherapy increased 2- to 3-year overall survival by an absolute 5.4 percent over chemotherapy alone (Warde and Payne, 1992; Pignon, Arrigada, Ihde, et al., 1992; Carney, 1999). Addition of TRTx to chemotherapy in patients with limited-stage SCLC is now the recommended course of therapy (Simon and Wagner, 2003). However, uncertainties remain with respect to optimal timing, sequencing, and radiation regimens (i.e., dosages and fractionation schemes) (Turrisi, 1994; Osterlind, 2001). Table 1 summarizes factors that might influence how chemotherapy and radiation may interact when used for primary treatment of limited stage SCLC.

Meta-analyses using different study inclusion criteria have addressed the timing of TRTx given with chemotherapy for limited-stage SCLC. Cancer Care Ontario (2003) included 5-year survival data for 4 studies involving 777 patients, finding no difference between early and late TRTx. Huncharek and McGarry compared the impact of early (i.e., given with the first or second course of systemic therapy) versus delayed (i.e., with the final courses) TRTx in patents with limited disease (Huncharek and McGarry, 2004). The analysis pooled data from 8 randomized, controlled trials enrolling over 1,500 patients and found that early, concurrent TRTx (i.e., administered during the same time period as chemotherapy) improved 1, 2, and 3-year overall survival relative to delayed TRTx, and that TRTx with etoposide/cisplatin regimens performed better compared with non-etoposide/cisplatin regimens. This meta-analysis was flawed by double-counting data from one study (i.e., Goto, Nishiwaki, Takada, et al. 1999 and Takada, Fukuoka, Kawahara, et al., 2002).

A meta-analysis by the Cochrane Collaboration (Pijls-Johannesma, De Ruysscher, Lambin, et al. 2004), included 7 studies, 6 of which overlapped with those in the Huncharek and McGarry meta-analysis, and found that the 2–3 year survival difference as a function of timing was less certain. The Cochrane meta-analysis identified patient selection issues and differences in systemic regimens as potential confounders. Fried, Morris, Poole, et al. (2004) included 7 studies with 1,500 patients and found that 2-year survival was significantly improved by early TRTx, but the pooled result was not significant at 3 years. Two-year subgroup analysis showed that using hyperfractionation and platinum chemotherapy were associated with significant advantages favoring early TRTx, but significant results were not obtained in studies using conventional fractionation and non-platinum chemotherapy.

The role of radiation therapy in extensive disease is less established than in patients with limited-stage disease (Murren, Turrisi, and Pass, 2005). Several large studies reported in the 1980s by the Southwest Oncology Group (SWOG) and that did not randomize patients to TRTx versus no TRTx, suggested that, although thoracic radiation reduced initial relapse at the primary tumor site, there was no effect on overall survival (Murren, Turrisi, and Pass, 2005; Livingston, Mira, Chen, et al., 1984; Livingston, Schulman, Mira, et al., 1986).

Prophylactic Cranial Irradiation. The frequency of brain metastasis in SCLC patients led to the hypothesis that subclinical metastases are commonly present in the brain at diagnosis. Thus, clinicians often add prophylactic cranial irradiation (PCI), particularly for patients achieving a complete remission (CR) after primary therapy. Without PCI, patients who achieve an extracranial CR have a 50–80 percent actuarial risk of developing CNS metastases within 2–3 years (Simon and Wagner, 2003; Murren, Turrisi, and Pass, 2005; Carney, 1999). In addition, among patients who achieve a CR with chemotherapy, approximately 15 percent have brain metastases as the initial or only manifestation of recurrence (Carney, 1999). A patient-level meta-analysis of almost 1,000 patients in complete remission from 7 randomized, controlled

Summary Table 1. Alternatives for Combined Chemotherapy and Radiation to Treat Limited SCLC

treatment variable	alternatives	known or possible advantages	known or possible disadvantages
chemotherapy regimen	platinum/etoposide (PE)	most effective regimen in multiple meta-analyses	relapse common despite initial high response rate
	cyclophosphamide- and/or doxorubicin-based (CD)	none known	response rates, survival inferior to PE
	alternating PE/CD	less likely to select PE-resistant cells for survival	uncertain; limits choices for 2nd-line therapy?
	PE + third (newer) drug	less likely to select PE-resistant cells for survival	increased toxicity without evidence of better survival
cumulative radiation dose (once daily fractions)	30 to 40 Gy	less normal tissue toxicity than larger doses	local failure rate ~80%
	>40 to 50 Gy	decreases local failure rate to 30–50%	increases normal tissue toxicity
	>50 to 65 Gy	may increase tumor kill, decrease local failure rate	further increases normal tissue toxicity
radiation target volume	larger volume (includes regional lymphatics)	may reduce regional failure rate	must limit total dose to avoid toxicity
	smaller volume (limited to involved fields)	smaller target permits larger dose; may decrease failure, yet avoid toxicity	tumor cells beyond target may survive, leading to relapse and progression
fraction size	>2 Gy per fraction	increases tumor cell kill per fraction	increases normal tissue acute and late toxicities
	≤2 Gy per fraction	permits delivering larger total dose in standard time without excess toxicity	reduces tumor cell kill per fraction
frequency of fractions	once daily	more convenient (patients) and efficient (facilities)	permits tumor cell repair (normal cells faster)
	hyperfractionation (≥2/day)	permits accelerated radiotherapy with equal or less toxicity	less convenient (patients) and efficient (facilities)
duration of radiation therapy	standard schedule: 4–6 weeks (≤10 Gy/week)	less risk for acute and late toxicity to normal tissues	radiation-resistant tumor cell clone may emerge
	accelerated schedule: ≤3 weeks (>10 Gy/week)	more effective for fast-growing tumors (e.g., SCLC); also permits dose escalation	may increase risk of acute and late toxicities
sequence of chemotherapy and radiation therapy	sequential	smaller radiation target if tumor shrinks; fewer radiation-resistant hypoxic tumor cells	sacrifices potential drug-radiation synergy
	concurrent	potential for synergy if one modality sensitizes cells to other's effects	may also synergize damage to normal cells (esophagus, bone marrow)
	alternating or split course	permits recovery from acute toxicity	permits tumor cells to repopulate
radiation timing relative to chemotherapy course	early cycles	less survival of chemotherapy resistant tumor cells	more hematopoietic toxicity
	late cycles	less hematopoietic toxicity	chemotherapy-resistant tumor cells may emerge

trials showed the addition of PCI can reduce the risk of CNS metastases by over half and significantly improves survival (Auperin, Arriagada, Pignon, et al. 1999; Prophylactic Cranial Irradiation Overview Collaborative Group, 2000; Carney, 1999).

Definitive recommendations regarding optimal timing of PCI and radiation dosage issues (e.g., optimizing dose to balance efficacy and toxicity, fractionation) still require additional study (Prophylactic Cranial Irradiation Overview Collaborative Group, 2000; Boher and Wenz, 2002). According to one of the PCI meta-analyses, "Establishing the optimal dose and timing of treatment so as to reduce further the incidence of brain metastases with minimal and acceptable toxicity should be the aim of future clinical trials" (Prophylactic Cranial Irradiation Overview Collaborative Group, 2000).

Data on the adverse effects of PCI, both acute (e.g., skin burns, headaches) and late-developing (e.g., neurocognitive impairment, overt cerebral necrosis) are also not well characterized from analyses of controlled trials (Boher and Wenz, 2002). Although many retrospective studies describe an association between PCI and neurotoxicity, evidence from prospective, controlled trials does not appear to support that association (Bohrer and Wenz, 2002).

Second-Line Therapy. Most patients respond to primary therapy, but relapse after remissions of varying duration (Murren, Turrisi, and Pass, 2005). Second-line therapy is offered to most patients if the first remission has lasted 3–6 months; relapse after 3 months or more is also known as "sensitive relapse" (Murren, Turrisi, and Pass, 2005). Evidence of benefit is lacking from second-line therapy for refractory SCLC (i.e., no remission after primary therapy). Response to second-line therapy appears to be related to the chemotherapy agents given in both the induction and second-line regimens (Murren, Turrisi, and Pass, 2005). It is also unknown whether third or subsequent lines of therapy for relapsed or progressive SCLC improve outcomes compared with best supportive care.

Key Questions for this Systematic Review

As stated previously, consultation with experts has identified critical concerns deserving of inquiry to support the ACCP update to guidelines on the diagnosis and management of lung cancer. Thus, this systematic review of the literature will address the following questions regarding managing patients with small cell lung cancer:

1. For limited-stage SCLC, what are the relative benefits and harms (survival, toxicity, and quality of life) of TRTx combined with chemotherapy either in alternating fashion, concurrently or sequentially?

2. For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is given in early versus late chemotherapy cycles?

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

- accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens (<10 Gy per week) versus split courses delivered over the standard interval; and

- single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation (PCI)?

6. Does the addition of PET scanning improve the accuracy of staging for patients diagnosed with SCLC, over the use of other techniques, including CT and MRI, without PET?

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Chapter 2. Methods

The objective of this Evidence Report is to systematically review and synthesize available evidence on managing patients diagnosed with small cell lung cancer (SCLC). The Key Questions addressed here were proposed by the American College of Chest Physicians, the partner organization for this evidence report and were refined after consultation with experts.

Peer Review

A technical expert group provided consultation for the systematic review. The draft report was reviewed by 10 external reviewers, including members of the technical expert group, the Task Order Officer, other invited technical experts, and stakeholders (Appendix E).* Revisions were made to the draft report based on reviewers' comments.

Study Selection Criteria

Types of Studies

All questions, except Question 6, addressed therapeutic interventions. We sought randomized, controlled trials that compared the interventions of interest. No minimum number of patients per study arm was required for randomized, controlled trials. Because there were few randomized, controlled trials available to address Questions 8 and 9, we sought additional studies. For Question 8 (surgery), we also sought nonrandomized comparative trials, both prospective and retrospective in design. For Question 9 (second- or subsequent-line therapy), we also sought phase II multicenter trials reporting on at least 25 patients.

Question 6 (PET for staging) addresses a diagnostic intervention. Although we sought randomized, controlled trials comparing the outcomes of SCLC patients staged with and without use of PET, no such studies were identified. We then sought prospective, single-arm trials that reported on at least 25 patients undergoing imaging to stage SCLC; correlated 18-fluorodeoxyyglucose (FDG) PET findings with findings from other imaging modalities and an appropriate reference standard; and permitted computation of sensitivity and specificity.

Our search and selection criteria included English-language studies, as well as foreign-language studies that had an English-language abstract.

Studies were excluded if no outcome of interest to this review was reported. Studies were also excluded if the patient population of interest was fewer than 80 percent of included patients, or, alternatively, results for the patient population of interest were not separately reported. When

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

multiple reports were available for the same study, it was counted as a single trial and outcome data from the report with the longest follow-up were used.

Types of Participants

- Key Questions 1–3 (First-line chemotherapy with thoracic radiotherapy [TRTx]) — patients with a histopathologically confirmed diagnosis of SCLC staged as limited disease.

- Key Question 4 (thoracic radiation therapy) — Patients with a histopathologically confirmed diagnosis of SCLC staged as extensive disease undergoing first-line therapy.

- Key Question 5 (prophylactic cranial irradiation) — Patients with a histopathologically confirmed diagnosis of SCLC that has completely responded to primary therapy (regardless of stage).

- Key Question 6 (PET staging) — Patients with a histopathologically confirmed diagnosis of SCLC.

- Key Question 7 (management mixed disease) — Patients with a histopathologically confirmed diagnosis of mixed small cell/non-small cell lung cancer.

- Key Question 8 (surgery) — Patients with a histopathologically confirmed diagnosis of SCLC staged as limited disease with small tumors and no nodal involvement

- Key Question 9 (second- or subsequent-line therapy) — Patients with a histopathologically confirmed diagnosis of SCLC that either relapsed or progressed after a response that lasted at least 3 months following primary therapy for: (a) limited-stage or (b) extensive-stage disease; or (c) patients with refractory disease (defined as no response or progression within 3 months of primary therapy).

Types of Interventions

- **Key Question 1** — Comparison of chemotherapy combined with sequential TRTx, chemotherapy combined with concurrent TRTx and chemotherapy combined with alternating TRTx.

- **Key Question 2** — Chemotherapy combined with concurrent TRTx initiated early cycles (i.e., 1 or 2) versus chemotherapy combined with concurrent TRTx initiated in late cycles (i.e., 3 or later).

- **Key Question 3** — Chemotherapy combined with standard-interval TRTx versus chemotherapy combined with accelerated TRTx: OR chemotherapy combined with split-course TRTx chemotherapy combined with standard-interval TRTx; OR chemotherapy combined with single daily fractions of TRTx; OR chemotherapy combined with hyperfractionated TRTx.

- **Key Question 4** — Chemotherapy combined with TRTx versus chemotherapy alone.

- **Key Question 5** — Prophylactic cranial irradiation (PCI) versus no prophylactic radiation after primary therapy is completed and response is assessed.

- **Key Question 6** — Positron-emission tomography (PET) vs. no PET, added to other staging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI).

- **Key Question 7** — Chemotherapy with or without TRTx delivered in any sequence or schedule used for limited-stage SCLC

- **Key Question 8** — Surgical excision of SCLC tumors, preceded by neoadjuvant chemotherapy or followed by adjuvant chemotherapy, and either with or without TRTx and PCI, versus no surgical excision

- **Key Question 9** — Chemotherapy using drugs approved by the U.S. Food and Drug Administration for at least one indication to treat a malignant disease (various regimens).

Types of Outcomes

Primary (health) outcomes of interest include:

- duration of survival, disease-free survival, and/or progression-free survival
- quality of life
- brain metastasis-free survival and subsequent treatment(s) for brain metastasis
- palliation of measurable symptoms
- treatment-related adverse events
- perioperative adverse events

Secondary (intermediate) outcomes include:

- objective response rates (complete and partial responses; separately and summed)
- response durations
- pathologically complete resection rates
- recurrence rates

For key question 6 (PET staging) additional outcomes of interest are:

- diagnostic accuracy
- outcomes other than diagnostic accuracy, such as staging accuracy, change in stage and impact on management decisions

Search Strategy and Review

Search Strategy

Electronic databases. The following databases were searched for citations. The full search strategy is displayed in Appendix A.* The search was not limited to English-language references, but foreign-language references without abstracts were disregarded.

- MEDLINE® (through 12/21/04)
- EMBASE (through 03/04/05)
- Cochrane Controlled Trials Register (through 03/11/05)

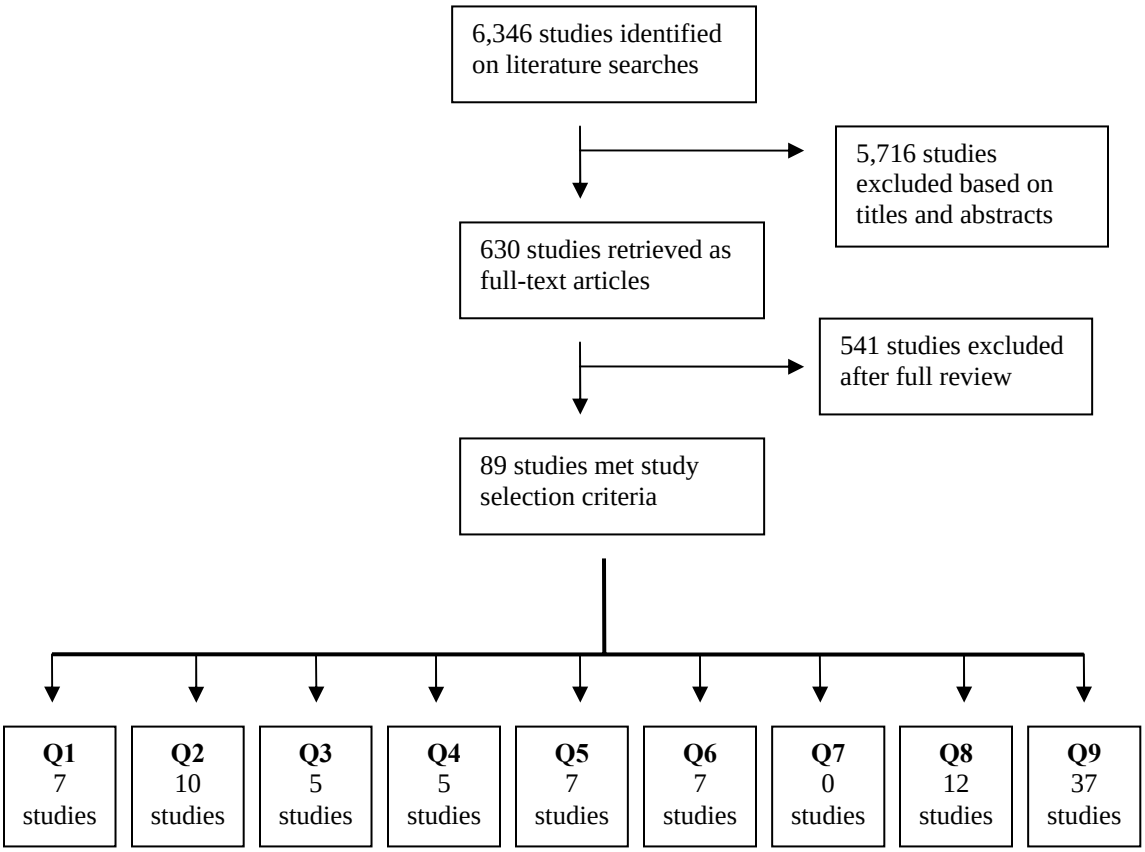
Additional Sources of Evidence. The Technical Expert Panel and individuals and organizations providing peer review were asked to inform the project team of any studies relevant to the key questions that were not included in the draft list of selected studies.

Search Screen

Search results were stored in a ProCite® database. Using the study selection criteria for screening titles and abstracts, a single reviewer marked each citation as either: (1) eligible for review as full-text articles; (2) ineligible for full-text review; or (3) uncertain. Citations marked as uncertain were reviewed by a second reviewer and resolved by consensus opinion, with a third reviewer to be consulted if necessary. Using the final study selection criteria, review of full-text articles was conducted in the same fashion to determine inclusion in the systematic review. A total of 630 references were retrieved at a full-text level; 89 were included in this review (Figure 1). Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review, were kept in the ProCite® database (see Appendix D, Excluded Studies).

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Figure 1. QUOROM Flow Diagram



Data Extraction and Analysis

Data Elements

The data elements below were abstracted, or recorded as not reported, from therapeutic intervention studies.

- critical features of the study design (for example, patient inclusion/exclusion criteria, number of subjects, use of blinding);
- potential patient characteristic confounders:
  - age
  - gender

    - race
    - extent of disease and stage
    - performance status
    - comorbidities
- treatment protocols (for example, treatment intensity, frequency, duration, other prior and concurrent treatment factors);
- patient monitoring procedures (for example, follow-up duration and frequency, outcome assessment methods); and
- the specified key outcomes and data analysis method (when statistical test results were lacking for adverse events data, reviewers performed tests with the STATMAN statistical program).

The data elements below were abstracted, or recorded as not reported, from diagnostic accuracy studies of imaging modalities used in staging SCLC:

- patient selection criteria
- details about the reference standard (validity and degree of detail in description)
- decision rules for determining which patients received the reference standard
- whether the index test and reference standard were interpreted blind to each other
- whether verification bias (index test results influenced decisions to perform reference standard) was avoided
- details about the index test (degree of detail about performing of test, interpretation)
- study design (prospective, retrospective)
- reporting of diagnostic accuracy results (completeness, appropriate calculation of accuracy measures, use of confidence intervals)
- outcomes other than diagnostic accuracy, such as staging accuracy, change in stage and impact on management decisions

Evidence Tables

Templates for evidence tables were created in Microsoft Excel® and Microsoft Word® Appendix B).* One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer reviewed the evidence tables for accuracy. Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occurred in quantitative estimates of data from published figures, the values obtained by the two reviewers were averaged.

Assessment of Study Quality

Therapeutic Studies

The general approach to grading evidence developed by the U.S. Preventive Services Task Force (Harris et al. 2001) was applied. Quality of the abstracted studies was assessed by one reviewer and fact-checked by a second. Discordant quality assessments were resolved by discussion or by consultation with a third reviewer, if necessary. The quality criteria for randomized, controlled trials were as follows:

- Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., baseline characteristics, other concomitant care) were distributed equally among groups
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders, intention-to-treat analysis

Diagnostic Studies

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool underwent a rigorous development process by Whiting, Rutjes, Dinnes, et al. (2004) and includes the following items:

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

- Was the spectrum of patients representative of the patients who will receive the test in practice?
- Were selection criteria clearly described?
- Is the reference standard likely to classify the target condition correctly?
- Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
- Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
- Did patients receive the same reference standard regardless of the index test result?
- Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
- Was the execution of the index test described in sufficient detail to permit replication of the test?
- Was the execution of the reference standard described in sufficient detail to permit replication of the reference standard?
- Were the index test results interpreted without knowledge of the results of the reference standard?
- Were the reference standard results interpreted without knowledge of the results of the index test?
- Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
- Were uninterpretable/intermediate test results reported?
- Were withdrawals from the study explained?

Definition of Ratings Based on Criteria

The rating of therapeutic intervention studies encompasses the 3 quality categories described below. No analogous quality categories have been incorporated into the QUADAS tool for assessing diagnostic accuracy studies. Rather, each of the 14 QUADAS items is considered individually.

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for randomized, controlled trials (RCTs), intention to treat analysis (i.e., all patients randomized were analyzed) is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

Meta-Analysis

Quantitative synthesis of evidence was carried out by combining studies meeting selection criteria for key questions 1 and 2. Eleven such randomized controlled trials (RCTs) could be viewed as comparing early and late thoracic radiotherapy (TRTx) for limited-stage small cell lung cancer (see "Results: Results of Meta-Analysis/Meta-Regression"). This Review defines early TRTx as given in cycles 1 or 2 and late as given in cycle 3 or later and at least 3 weeks after the start of early TRTx. Of the 11 RCTs, all provide 3-year overall survival data and 9 give 2-year data. The metrics used in the meta-analysis were 2-year and 3-year mortality relative risks (RRs). Estimates of survival were multiplied by sample sizes and rounded to the nearest whole number to derive the numbers alive and dead at 2 years and 3 years. While this method has been used in 4 previous meta-analyses on the timing of TRTx for limited SCLC, it does not take into account censoring and therefore may inflate subject counts. Even if a consensus method to incorporate censoring was available, it could not be applied to 6 of 11 studies due to insufficient detail in articles. Our method assures easy comparisons with previous meta-analyses and inclusion of more studies.

Meta-analysis was not worth pursuing for other questions in this Review. For key questions 3, 4, 7, 8, and 9, there was either an inadequate number of studies or excessive heterogeneity of treatments for pooled analysis. Question 5 was the subject of a recent patient-level meta-analysis (Auperin, Arriagada, Pignon, et al. 1999; Prophylactic Cranial Irradiation Overview Collaborative Group, 2000; Carney, 1999) and thus, a meta-analysis was not necessary for this Review. Uncertainty about the reference standard used in studies on question 6 was so great that a meta-analysis could give unwarranted weight to uniformly poor quality studies.

The first step in the meta-analysis was to assess whether publication bias was likely. This was first done visually with funnel plots, in which the trials are sorted along the vertical axis in ascending order of the standard error of the log odds ratio. A formal test for publication was performed using Egger's linear regression (Egger, Davey Smith, Schneider, et al., 1997). Trial standardized effect estimates were fit to precision values (the inverse of the standard error), using least squares and trial's inverse variance as weights. Asymmetry suggestive of publication bias would be indicated by a regression intercept value that significantly deviates from zero.

The next step in the meta-analysis is to determine whether significant heterogeneity of treatment effects exists. A standard test for heterogeneity is the Q statistic (Cochran, 1954). The null hypothesis of homogeneity is rejected below an alpha level of 0.10. If rejected, the combined RR point estimate should be computed with a random effects (RE) model (DerSimonian and Laird, 1986). Where necessary, the between-study variance component (tau squared) was calculated using the algebraic method described by Sutton, Abrams, Jones, et al. (2000). If the null hypothesis of homogeneity is not rejected, a fixed effects (FE) model would be used (Cochran, 1937).

Pooled estimates of treatment effects were derived using the inverse variance-weighted method (Cochran, 1937). Meta-analysis results are presented graphically in forest plots. Subgroup/sensitivity analyses were performed for these variables: whether early TRTx was given at the earliest opportunity; whether hyperfractionation was used; whether platinum was included in chemotherapy (CTx); whether early TRTx was given concurrent with CTx; and whether the trial was rated as being of good quality. Influence analysis was conducted by excluding each trial individually to reveal the impact on effect estimates. Results are presented graphically.

Random effects meta-regression, as described by Berkey, Hoaglin, Mosteller, et al. (1995), was conducted to explore sources of heterogeneity. All covariates are dichotomous variables, the same variables as those in subgroup/sensitivity analyses. Single variables were tested first. Multiple variables were included only as an exercise due to concerns of overfitting. Analyses were carried out using STATA 9.0 and Microsoft Excel 2002.

Chapter 3. Results

Key Question 1

For limited-stage small cell lung cancer (SCLC), what are the relative benefits and harms (survival, toxicity, and quality of life) of thoracic radiotherapy (TRTx) combined with chemotherapy, either in alternating fashion, concurrently or sequentially?

This question concerns how TRTx is given in relation to chemotherapy. Alternating TRTx is administered between chemotherapy cycles. Concurrent TRTx is TRTx given at the same time as chemotherapy. Sequential TRTx is given after completion of chemotherapy.

Overview

As summarized in Summary Table 2, 6 randomized, controlled trials (RCTs) made comparisons of alternating, concurrent and sequential TRTx for limited stage SCLC. Two trials (n=307) compared concurrent and sequential TRTx (Takada, Fukuoka, Kawahara, et al., 2002; Park, Kim, Jeong, et al., 1996). Two trials compared alternating to sequential TRTx (Gregor, Drings, Burghouts, et al., 1997; Sun, Zhang, Yin, et al., 1995; n=458). One trial compared alternating to concurrent TRTx (Lebeau, Urban, Brechot, et al., 1999, n=156). The Work and colleagues trial (Work, Nielsen, Bentzen, et al., 1997/Work, Bentzen, Nielsen, et al., 1996) compared early alternating and late alternating TRTx (n=199). Collectively, the 6 trials randomized 228 patients to concurrent treatment, 337 patients to alternating treatment, and 385 patients to sequential treatment. It is worth noting that these studies were generally small in size and likely underpowered to find small but clinically significant differences in survival.

Study populations and treatment protocols are summarized in Summary Table 3. Additional details are in Appendix Tables 1A–D, 1H.[*] Information in the tables came exclusively from articles except for the Park, Kim, Jeong, et al. (1996) study. Park, Kim, Jeong, et al. (1996) did not report survival probabilities at yearly intervals, so an author was contacted directly and additional data were sought. The data obtained from the author represented a larger patient sample than described in the article.

Concurrent vs. Sequential

Interventions. Two trials compared concurrent and sequential TRTx. Radiation dose in the Takada, Fukuoka, Kawahara, et al. (2002) study was 45 Gy, while it varied between 40 and 50 Gy in the Park, Kim, Jeong, et al. (1996) study. Both studies gave concurrent TRTx in weeks 1-3. Sequential TRTx occurred in weeks 13-15 in the Takada, Fukuoka, Kawahara, et al. (2002) trial and between weeks 19 and 24 in the Park, Kim, Jeong, et al. (1996) study. Takada, Fukuoka, Kawahara, et al. (2002) delivered 2 daily fractions of TRTx in both groups, while Park, Kim, Jeong, et al. (1996) gave it to the concurrent group. Both studies gave prophylactic cranial

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

irradiation (PCI). Platinum-based chemotherapy was used by Park, Kim, Jeong, et al. (1996), but not by Takada, Fukuoka, Kawahara, et al. (2002).

Summary Table 2. Overall Summary of Question 1 Trials

Study	Treatment arm	Control arm	Treat-ment n	Control n	Pt?	CTx	TRTx Dose (Gy) #Fracs /d	TRTx Timing		PCI ?	Quality Rating
								Tx	Control		
Takada, Fukuoka, Kawahara, et al., 2002 Multicenter	concurrent	sequential	114	114	yes	PE	45 2/d	wk 1-3	wk 13-15	yes	Good
Park, Kim, Jeong, et al., 1996 Single center	concurrent	sequential	32	47	yes	CAV-CbPE	40-50 2/d,1/d	wk 1-3	wk 19-24	yes	Poor
Sun, Zhang, Yin, et al., 1995 Multicenter	alternating	sequential	64	59	no/ yes	COM E, CE-CAP	30-60 1/d	wk 4-9	wk 13-18	?	Poor
Gregor, Drings, Burghouts, et al., 1997 Multicenter	alternating	sequential	170	165	no	CAE	50 1/d	wk 7,11, 15,19	wk 15-18	?	Good
Lebeau, Urban, Brechot, et al., 1999 Multicenter	alternating	concurrent	74	82	no	CAE-CVE	55/50 1/d	wk 6-7, 10-11, 14-16	wk 5-9	yes	Good
Work, Nielsen, Bentzen, et al. 1997/Work, Bentzen, Nielsen, et al., 1996 Single center	early alternating	late alternating	99	100	yes	CAV-PE	40-45 1/d	wk 1-2, 6-7	wk 18-19, 23-24	yes	Fair

Abbreviations table provided at the end of the Report.

Summary Table 3. Sample and Treatments: Alternating, Concurrent, or Sequential Radiotherapy

Study	n		Age	% Female	% Performance Status				CTx Regimen	RTx Regimen		
Gregor, Drings, Burghouts, et al., 1997 EORTC LCCG Multiple European institutions, 3/89 -1/95	Total	335	md (rng)		0	1	2	3		Dose	Schedule	PCI?
	Seq	165	61 (33-75)	32.1	46.1	47.9	4.2	1.8	CAE	50 Gy	wks 15-18, 20 frac, 1/d, 5/wk	possible if CR
	Alt	170	61 (34-74)	34.1	47.1 ECOG	44.7	5.9	2.4	same	50 Gy	wks 7, 11, 15, 19; 20 frac, 1/d, 5/wk	same
Lebeau, Urban, Brechot, et al., 1999 26 French institutions, 5/88 – 5/94	Total	156	mn		0	1	2-3	NR		Dose	Schedule	PCI?
	Alt	74	58	14.9	50.0	44.6	4.1	1.4	CAE-CVE	55 Gy	wks 6-7, 10-11, 20 Gy, 8 frac, 12 d, wks 14-15, 15 Gy, 6 frac, 10 d	if CR
	Conc	82	57	20.7	51.2 ECOG	46.3	2.4	0.0	same	50 Gy	wks 5-9, 40 Gy, 16 frac, 7 d	same
Takada, Fukuoka, Kawahara, et al., 2002 15 Japanese institutions, 5/91 - 1/95	Total	228	md (rng)		0	1	2			Dose	Schedule	PCI?
	Seq	114	64 (30-74)	18.4	28.9	65.8	5.3		PE	45 Gy	wks 13-15, 30 frac, 2/d, 5/wk	if CR, near-CR
	Conc	114	65 (39-74)	20.2	21.9 ECOG	72.8	5.3		same	45 Gy	wks 1-3, 30 frac, 2/d, 5/wk	sane
Sun, Zhang, Yin, et al., 1995 15 Chinese institutions, 1983 -1989	Total	123								Dose	Schedule	PCI?
	Seq	59							COME, CE-CAP	45-60 Gy 30-45 Gy	Local dis, after 2 CTx cyc, 6 wks MS/SC LNs, 3-4 wks	not specified
	Alt	64							Same	45-60 Gy 30-45 Gy	Local dis, between 2 CTx cyc, 6 wks MS/SC LNs, 3-4 wks	

Abbreviations table provided at the end of the Report.

Summary Table 3. Sample and Treatments: Alternating, Concurrent, or Sequential Radiotherapy (continued)

Study	n		Age	% Female	% Performance Status				CTx Regimen	RTx Regimen		
Work, Nielsen, Bentzen, et al. 1997/Work, Bentzen, Nielsen, et al., 1996 single-center study, 3/81-9/89	Total	199	md (rng)		100	90-80	70-60	50-40		Dose	Schedule	PCI?
	L Alt	100	59 (36-69)	29	10.0	70.0	15.0	5.0	CAPE	40-45 Gy	wks 18-19, 23-24, 1 frac/d	all
	E Alt	99	61 (36-70)	45	13.1 KPS	68.7	14.1	4.0	Same	40-45 Gy	wks 1-2, 6-7, 1 frac/d	same
Park, Kim, Jeong, et al., 1996 Korean Center 5/91 – 5/96	Total	51	mn (sd)		0	1	2			Dose	Schedule	PCI?
	Seq	24	60.6 (8.9)	20.8	25.0	45.8	29.2		CAV-CbPE	40-50 Gy	wks 19-24, 1 frac/d	if CR maintained
	Conc	27	57.5 (8.8)	14.8	14.8	63.0	22.2		Same	45 Gy	wks 1-3, 2 frac/d	same

Populations. Groups were well-balanced on age, gender and performance status in the Takada, Fukuoka, Kawahara, et al. (2002) study (n=228). The sample of 51 patients in the Park, Kim, Jeong, et al. (1996) article was also well-balanced on these characteristics, but the survival data represented 79 patients and no comparison of baseline characteristics is available for all.

Quality and Reporting. The Takada, Fukuoka, Kawahara, et al. (2002) trial was rated as being of good quality. The Park, Kim, Jeong, et al. (1996) study was rated as poor due to insufficient information about assembly and maintenance of comparable groups, in addition to uncertainty about full accounting of subjects in data analysis.

Results. Survival outcomes are shown in Summary Table 4 and adverse events in Summary Table 5. More detailed results are in Appendix Tables 1E-1G.* Both studies showed survival results favoring concurrent TRTx, but were generally not statistically significant. Unadjusted overall survival did not differ significantly between concurrent and sequential TRTx, although p values were nearly significant. Overall median survival favored concurrent therapy by 5.1 months (Park, Kim, Jeong, et al., 1996) and 7.5 months (Takada, Fukuoka, Kawahara, et al., 2002). A Cox proportional hazards model regression found that treatment was a significant predictor of survival, producing a hazard ratio of 0.70 (95 percent confidence interval [CI]: 0.52–0.94) for concurrent relative to sequential TRTx. Takada, Fukuoka, Kawahara, et al. (2002) also reported that median progression-free survival favored the concurrent group by 2 months (p=0.084), but Park, Kim, Jeong, et al. (1996) did not report on progression.

Neither study reported on quality of life, but both reported tumor response data. Both found nonsignificantly higher overall response rates (ORRs) in the concurrent group, although the Park, Kim, Jeong, et al. (1996) study found a fairly large difference in rates that approached significance. In the Takada, Fukuoka, Kawahara, et al., 2002) study, ORRs were 96.5 percent; for concurrent and 92.1 percent for sequential (p=0.25). The complete responses (CRs) were higher in the concurrent group (39.5 percent) than in the sequential group (27.2 percent, p=0.07). In the Park, Kim, Jeong, et al. (1996) trial, the concurrent group achieved an ORR of 88 percent, versus 63 percent for sequential (p=0.13). Mean response duration was longer in the sequential group than in the concurrent group (395 days vs. 180 days, p=0.03).

Among 12 categories of adverse events, 5 were reported by both studies (Summary Table 6). Significant between-group differences were not found in either trial for anemia, thrombocytopenia, infection and fever. Both studies found significantly higher risks of leukopenia for those in the concurrent arm. In the Takada, Fukuoka, Kawahara, et al. (2002) study, grade 3 or 4 leukopenia was seen in 88.4 percent of concurrent-arm patients and in 53.6 percent of sequential-arm patients (p=0.001). The risk of higher grade leukopenia among concurrent TRTx patients in the Park, Kim, Jeong, et al. (1996) study was 51.8 percent, compared with 16.7 percent of sequential TRTx patients (p=0.02). One study reported data on each of 7 adverse events, none of which was marked by significant differences between concurrent and sequential TRTx: treatment-related mortality, nausea/vomiting, esophagitis, renal toxicity; alopecia, arrhythmias, and hepatic toxicity.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf

Summary Table 4. Survival Outcomes: Alternating, Concurrent and Sequential Radiotherapy

Study	N		OS Md (mo)	1 yr	2 yr	3 yr	4 yr	5 yr	PFS Md (mo)	1 yr	2 yr	3 yr	4 yr	5 yr
Gregor, Drings, Burghouts, et al., 1997	Seq	165	15	64%	23%	15%	~14%	~12%	12	50%	22%	17%	15%	5%
	Alt	170	14	60%	26%	12%	~10%	~4%	10	43%	16%	10%	8%	8%
	Difference:		-1	-4%	3%	-3%	-4%	-8%	-2	-7%	-6%	-7%	-7%	3%
			(CPHM: RR 0.88, 95% CI 0.68-1.1, p=0.237; p=0.288, log-rank)						(Log-rank p=0.07)					
Lebeau, Urban, Brechot, et al., 1999	Alt	74	14.0	63%	17%	11%	6%	6%						
	Conc	82	13.5	54%	13%	6%	4%	4%						
	Difference		-0.5	-9%	-4%	-5%	-2%	-2%						
			(p=0.15, log-rank, 66 Alt deaths, 77 Conc deaths)											
Takada, Fukuoka, Kawahara, et al., 2002	Seq	114	19.7	~80%	35.1%	20.2%	~20%	18.3%	~10	~38%	~19%	~15%	~14%	~14%
	Conc	114	27.2	~80%	54.4%	29.8%	~25%	23.7%	~12	~50%	~28%	~25%	~20%	~17%
	Difference		7.5	0%	19.3%	9.6%	5%	5.4%	2	12%	9%	10%	6%	3%
			(p=0.097 eligible patients, p=0.086 all randomized, log-rank; CPMH: HR 0.70, 95% CI 0.52-0.94, p=0.02)						(p=0.084, log-rank))					
Sun, Zhang, Yin, et al., 1995	Seq	59		64.0%	13.6%	12.0%								
	Alt	64		62.5%	28%	16.0%								
	Difference			-1.5%	14.4%	4%								
Work, Nielsen, Bentzen, et al. 1997/Work, Bentzen, Nielsen, et al., 1996	L Alt	100	12.0	~49%	18.8%	~12%	~12%	12.0%	NR ~15	~58%	31.7%	~27%	~27%	27%
	E Alt	99	10.5	~43%	20.2%	~13%	~12%	10.8%	NR ~9	~42%	27.7%	25%	23%	23%
	Difference		-1.5	-6%	1.4%	1%	0%	-1.2%		-18%	-4%	0.2%	3.2%	2.8%
			(p=0.41, not significant, RR 0.88, 95% CI 0.66-1.08)						(PWIFR, HR 0.79, 95% CI 0.56-1.12)					
Park, Kim, Jeong, et al., 1996	Seq	47	16.0	74.4%	27.7%	8.8%	4.4%	2.2%						
	Conc	32	18.4	81.3%	29.0%	13.8%	10.7%	7.4%						
	Difference		2,4 (p=0.11)	6.9%	1.3%	5.0%	6.3%	5.2%						

Abbreviations table provided at the end of the Report.

Summary Table 5. Adverse Events: Alternating, Concurrent, or Sequential Radiotherapy

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Treatment-related mortality	Lebeau 1999	Deaths from aplasia	Alt	74	2.7	Conc	82	3.7	0.67	Gregor 1997; Sun 1995; Work 1997/1996; Park, 1996
		Deaths from pulmonary fibrosis	Alt	74	1.4	Conc	82	7.3	0.05	
	Takada 2002		Seql	110	3.6	Conc	112	2.7	0.72	
	Work 1997		L Alt	100	0	E Alt	99	0	1.00	
Nausea/Vomiting	Gregor 1997	Or vomiting, acute (WHO grade)								Lebeau 1999; Sun 1995; Work 1997/1996; Park, 1996
		0	Seql	165	25.5	Alt	169	36.1	0.129	
		1			21.8			21.3		
		2			37.6			25.4		
		3			13.3			15.4		
		4			0.6			1.2		
		NR			1.2			0.6		
	Takada 2002	Or vomiting (WHO grade ≥ 3)	Seql	110	19.1	Conc	112	10.7	0.09	
Anorexia										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
Lethargy										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
Neurosensory	Work 1997/1996	Moderate neurotoxicity (grade ≤ 3)	in 11 (of 199); no difference between groups							Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Park, 1996
Hearing loss										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
Esophagitis	Gregor 1997	Acute (WHO grade)								Lebeau 1999; Sun 1995; Work 1997/1996; Park, 1996
		0	Seql	165	83.0	Alt	169	75.7	0.198	
		1			7.9			11.8		
		2			6.1			9.5		
		3			3.0			3.0		
		Late esophageal stenosis (WHO grade)	Seql	143	82.5	Alt	135	94.1	0.010	
		0			11.2			3.0		
		1			2.8			1.5		
		2			2.1			0.7		
		3			1.4			0.7		
		NR								
	Takada 2002	WHO grade ≥ 3	Seql	110	3.6	Conc	112	8.9	0.17	

Abbreviations table provided at the end of the Report.

Summary Table 5. Adverse Events: Alternating, Concurrent, or Sequential Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Bronchopulmonary	Gregor 1997	Late Lung fibrosis (RTOG grade)								Takada 2002; Sun 1995; Work 1997/1996; Park, 1996
		0	Seql	143	19.6	Alt	135	11.1	0.135	
		1			19.6			20.0		
		2			21.7			27.4		
		3			18.2			14.8		
		4			18.9			24.4		
		NR			2.1			2.2		
	Lebeau 1999	Pulmonary fibrosis	Alt	74	2.7	Conc	82	8.5	0.17	
Pneumonitis										Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995; Work 1997/1996; Park 1996
Kidney	Work 1997/1996		quantified by chromium-edathamil clearance; did not differ between groups							Lebeau 1999; Gregor 1997; Takada 2002; Sun 1995
	Park 1996	ECOG grade 3	Seql	24	0	Conc	27	0	1.00	
		ECOG grade 4			0			0		
Anemia	Takada 2002	WHO grade 3	Seql	110	41.8	Conc	112	53.6	0.08	Lebeau 1999; Gregor 1997; Sun 1995; Work 1997/1996
	Park 1996	ECOG grade 3	Seql	24	0	Conc	27	3.7	1.00	
		ECOG grade 4			0			0		
Thrombocytopenia	Gregor 1997	Acute (WHO grade)								Lebeau 1999; Sun 1995;
		0	Seql	165	55.2	Alt	169	24.9	<0.001	
		1			13.9			17.2		
		2			10.9			23.1		
		3			12.7			11.8		
		4			6.7			20.7		
		NR			0.6			2.4		
	Takada 2002	(WHO grade)								
		3	Seql	110	12.7	Conc	112	29.5	0.11	
		4			13.6			7.1		
		$\geq$ 3			26.4			36.6		
	Work 1997/1996	WHO grades 3 & 4	L Alt	100	13	E Alt	99	13	1.00	
	Park 1996	ECOG grade 3	Seql	24	0	Conc	27	0	1.00	
		ECOG grade 4			0			3.7		

Summary Table 5. Adverse Events: Alternating, Concurrent, or Sequential Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Group	n	%	Group	n	%	p	Not Reporting
Leukopenia or neutropenia	Gregor 1997	Acute leukopenia (WHO grade) 0 1 2 3 4 NR	Seql	165	6.7 5.5 10.9 34.5 41.8 0.6	Alt	169	4.1 1.2 3.6 17.8 71.6 1.8	<0.001	Sun 1995
	Lebeau 1999	Neutropenia (grade 3 or 4)	Alt	74	60.8	Conc	82	58.5	0.87	
	Takada 2002	Leukopenia (WHO grade) 3 4 3 or 4	Seql	110	44.5 9.1 53.6	Conc	112	50.9 37.5 88.4	0.001	
	Work 1997/1996	WHO grades 3 & 4 leukopenia WHO grade 4 leukopenia	L Alt	100	39 6	E Alt	99	67 23	<0.001 0.0006	
	Park 1996	Leukopenia ECOG grade 3 ECOG grade 4	Seql	24	12.5 4.2	Conc	27	40.7 11.1	0.0176	
Infection	Takada 2002	WHO grade ≥3	Seql	110	0.9	Conc	112	5.4	0.12	Lebeau 1999; Gregor 1997; Sun 1995
	Work 1997/1996		neutropenic fever in 8 patients; no difference between groups							
	Park 1996	ECOG grade 3 ECOG grade 4	Seql	24	0 0	Conc	27	3.7 0	1.00	
Other	Takada 2002	Alopecia (WHO grade ≥3)	Seql	109	12.7	Conc	109	11.6	0.99	
	Takada 2002	Fever (WHO grade ≥3)	Seql	110	1.8	Conc	112	1.8	0.99	
	Takada 2002	Arrhythmias (WHO grade ≥3)	Seql	110	0.0	Conc	112	1.8	0.50	
	Park 1996	Hepatic ECOG grade 3 Hepatic ECOG grade 4	Seql	24 0	0	Conc	27 0	0	1.00	

Summary Table 6. Adverse Events Reported in Takada and Park Trials

Adverse Event	Takada	Park
Treatment-related Mortality		NR
Nausea/vomiting		NR
Esophagitis		NR
Anemia		
Thrombocytopenia		
Leukopenia	▲	▲
Kidney	NR	
Infection		
Fever		
Alopecia		NR
Arrhythmias		NR
Hepatic	NR	

▲=significantly more frequent in concurrent than in sequential arm; ▼=significantly less frequent in concurrent than in sequential arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. These 2 studies suggest better efficacy outcomes for concurrent TRTx than for sequential TRTx, with inconsistent statistical significance, along with similar rates of adverse events of all types except leukopenia, which was more common for concurrent TRTx. Unadjusted analyses of overall survival found nearly significant differences favoring concurrent over sequential TRTx in 2 studies. One study using adjustment by Cox regression found a significant treatment effect for concurrent TRTx. One study that analyzed progression-free survival reported a nearly significant difference in favor of concurrent TRTx. CRs were more common with concurrent therapy in both studies, but not significantly so (p values were 0.07 and 0.13). One study found a significantly longer response duration for concurrent TRTx. Only 1 of 11 types of adverse events showed significant between-group differences. Leukopenia was more common for concurrent TRTx in both studies.

Alternating vs. Sequential

Interventions. Both Sun, Zhang, Yin, et al. (1995) and Gregor, Drings, Burghouts, et al. (1997) delivered TRTx in single fractions per day. There was a wide range of total doses in the Sun, Zhang, Yin, et al. (1995) study (30–60 Gy), while the Gregor, Drings, Burghouts, et al. (1997) study gave 50 Gy to all patients. Alternating TRTx was given between weeks 4 and 9 in the Sun, Zhang, Yin, et al. (1995) study, whereas Gregor, Drings, Burghouts, et al. (1997) administered it every 4 weeks between 7 and 20 weeks. In the Gregor, Drings, Burghouts, et al. (1997) study, 4 weeks of TRTx in the alternating arm was given over a period of 13 weeks

wherease sequential TRTx was given over 4 consecutive weeks. Sun, Zhang, Yin, et al. (1995) provided TRTx over 6 consective weeks in both the alternating and sequential arms. That study also used platinum-based chemotherapy in the later period of the trial, but no patients received it in the Gregor, Drings, Burghouts, et al. (1997) study. Neither report made clear whether patients received PCI.

Populations. The Sun, Zhang, Yin, et al. (1995) article did not report any baseline patient characteristics; it simply stated that 123 patients had localized disease. Patient groups in the Gregor, Drings, Burghouts, et al. (1997) study (n=335) were well-matched on the 3 key characteristics: age, gender and performance status.

Quality and Reporting. Gregor, Drings, Burghouts, et al. (1997) received a good study quality rating. Sun, Zhang, Yin, et al. (1995) was rated as poor because details were lacking for all quality domains.

Results. Gregor, Drings, Burghouts, et al. (1997) did not find a statistically significant difference between groups in adjusted survival. Median survival was 15 months in the sequential group and 14 months in the alternating group. The entire survival curve for the sequential TRTx group was slightly higher than that of the alternating group. Between 1 and 4 years, survival probabilities differed by 4 percent or less, while the difference was 8 percent at 5 years. In the Sun, Zhang, Yin, et al. (1995) study, statistical test results for survival were missing. At 1 year, the survival probability was higher in the sequential group by 1.5 percent, whereas at 2 an 3 years, it was higher for the alternating group by 14.4 percent and 4 percent. Relative risks (RR) for death at 2 years and 3 years were computed for purposes of meta-analysis. At 2 years, the RR of 0.831 significantly favors alternating TRTx (95 percent CI: 0.692–0.999). The difference is smaller and in the same direction at 3 years, with an RR of 0.957, but nonsignificant (95 percent CI: 0.831–1.102). The difference in progression-free survival favoring sequential TRTx in the Gregor, Drings, Burghouts, et al. (1997) study approached statistical significance (p=0.07). Neither study reported on tumor response or quality of life.

Sun, Zhang, Yin, et al. (1995) reported no data on adverse events (Summary Table 7), while Gregor, Drings, Burghouts, et al. (1997) gave data on 6 types. There were no between-group differences in the incidence of nausea/vomiting, acute esophagitis, or late pulmonary fibrosis. Late esophagitis was significantly less frequent in the alternating group, compared to the sequential group (p=0.01). Both thrombocytopenia and leukopenia were more common ($p<0.001$) in the alternating group.

Summary Table 7. Adverse Events Reported in Gregor and Sun Trials

Adverse Event	Gregor	Sun
Nausea/vomiting		NR
Acute Esophagitis		NR
Late Esophagitis	▼	NR
Late Pulmonary Fibrosis		NR
Thrombocytopenia	▲	NR
Leukopenia	▲	NR

▲=significantly more frequent in alternating than in sequential arm; ▼=significantly less frequent in alternating than in sequential arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. Results are mixed on the relative impact on outcomes for alternating and sequential TRTx. One study reported that the survival curve for sequential TRTx was always higher than that for alternating TRTx, but the difference was not significant. The other study showed a significant difference in the RR of death at 2 years favoring alternating TRTx. The study reporting progression-free survival found a nearly significant advantage for sequential TRTx. Late esophagitis was more common for the sequential group, but thrombocytopenia and leukopenia were more frequent in the alternating group. These data do not show a clear advantage for either sequential or alternating TRTx.

Alternating vs. Concurrent

Interventions. The Lebeau, Urban, Brechot, et al. (1999) study delivered doses of 55 Gy to the alternating TRTx group and 50 Gy to the concurrent TRTx group.[*] Radiation was given in once daily fractions to both groups. Concurrent TRTx was offered across 5 weeks from week 5 through 9, while alternating TRTx occurred across 11 weeks during weeks 6–7, 10–11 and 14–16. Both groups received PCI. Non-platinum chemotherapy was administered.

Populations. The 2 groups of patients in this study (n=156) were well-matched on baseline characteristics.

Quality and Reporting. This trial received a good study quality rating.

[*] During final preparation of this report, a second comparison was published of concurrent versus alternating TRTx (Blackstock, Bogart, Matthews, et al., 2005). The study compared five weeks of continuous radiation concurrent with chemotherapy cycles 1-2 (n=56) versus split-course alternating radiation given during weeks without chemotherapy in cycles 1-3 (n=54). Overall survival did not differ between the two groups (median, 14 versus 15 months; survival at 2 years, 36% versus 31%; survival at 5 years 18% versus 17%). Since radiation began in week 1 for the continuous arm and in week 2 for the alternating arm, this study did not meet inclusion criteria for meta-analysis of early versus late radiation therapy.

Results. The entire survival curve for alternating TRTx lies slightly above that for concurrent TRTx, but the difference overall was not significant. Differences in survival probabilities ranged from a high at 1 year of 9 percent to a low of 2 percent at 5 years. Progression-free survival and quality of life was not reported. There was no statistically significant difference between groups in tumor response rates.

Four types of adverse events (Summary Table 8) were noted by Lebeau, Urban, Brechot, et al. (1999). The only outcome that showed a statistically significant between-group difference was deaths from pulmonary fibrosis, which were more common in the concurrent TRTx group (p=0.05).

Summary Table 8. Adverse Events Reported in Lebeau Trial

Adverse Event	Lebeau
Deaths from aplasia	
Deaths from Pulmonary Fibrosis	▲
Pulmonary Fibrosis	
Neutropenia	

▲=significantly more frequent in concurrent than in alternating arm; ▼=significantly less frequent in concurrent than in alternating arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. The single study comparing alternating and concurrent TRTx does not suggest a meaningful improvement in survival associated with alternating TRTx. Overall survival did not differ significantly, with a difference between medians of only 0.5 months favoring alternating TRTx. Deaths from pulmonary fibrosis were more frequent in the concurrent TRTx group.

Early Alternating vs. Late Alternating

Interventions. The dose given to both groups in the early phase of the Work and colleagues study (Work, Nielsen, Bentzen, et al., 1997/Work, Bentzen, Nielsen, et al., 1996) was 40 Gy; it was increased later to 45 Gy. Radiation was delivered as a single daily fraction in both treatment arms. TRTx was given during weeks 1–2 and 6–7 in the early-alternating group and in weeks 18–19 and 23–24 in the late-alternating group. Given the somewhat lower total dose in this study compared with other studies addressed above and administration in split-course fashion, TRTx was given at a relatively low dose rate. Both groups received PCI. The chemotherapy regimen for all patients was platinum-based; however the regimen was given in an unusual schedule and the doses of drugs actually delivered is unclear..

Populations. Groups receiving early and late alternating TRTx were well-balanced on baseline patient characteristics.

Quality and Reporting. This study was rated as fair in quality. The key deficiency was an inadequate description of the randomization method.

Results. Work and colleagues (Work, Nielsen, Bentzen, et al., 1997/Work, Bentzen, Nielsen, et al., 1996) reported that median survival was slightly longer in the late-alternating group (1.5 months), while 2- and 3-year survival probabilities were slightly higher in the early-alternating group. Overall, there was no significant difference in survival between groups. There was an 18 percent difference at 1 year in percentage without in-field recurrence (PWIFR) favoring late-alternating TRTx, but differences at later times were much smaller and the groups did not differ significantly. Tumor response rates did not differ for the 2 patient groups. No quality of life data were collected.

Of the 6 categories of adverse events, only leukopenia showed a difference between groups (Summary Table 9). This outcome was significantly more common among those receiving early alternating TRTx.

Summary Table 9. Adverse Events Reported in Work Trial

Adverse Event	Work
Treatment-related Mortality	
Neurotoxicity	
Kidney	
Thrombocytopenia	
Leukopenia	▲
Infection	

▲=significantly more frequent in early alternating than in late alternating arm; ▼=significantly less frequent in early alternating than in late alternating arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Summary. The single study comparing early and late alternating is does not support conclusions about the relative effectiveness of these approaches to TRTx. There was no significant difference between groups on overall survival, percentage without in-field recurrence and tumor response. Of 6 types of adverse events reported, groups differed only in the frequency of leukopenia, which was significantly higher among those receiving early alternating TRTx.

Conclusions

Among 6 studies meeting selection criteria for Key Question 1, two trials (n=307) compared concurrent and sequential TRTx. Two trials compared alternating to sequential TRTx (n=458).

One trial compared alternating to concurrent TRTx (n=156). The final trial compared early alternating and late alternating TRTx (n=199). Comparing these trials with others addressing TRTx delivery, survival is generally lower is this set relative to studies assessing the effect of hyperfractionation. Although an explanation is not readily apparent, possible reasons include patient selection, stage drift and the adequacy of chemotherapy.

Concurrent vs. Sequential. Results are not conclusive but suggest better outcomes for concurrent TRTx. Although not statistically significant, unadjusted overall survival and CR rates favored concurrent TRTx in both studies. However, adjusted overall survival in the larger study was significantly in favor of concurrent TRTx. A smaller study found significantly longer response duration for concurrent TRTx in 1 study. Out of 11 types of adverse events, only leukopenia occurred significantly more frequently, in the concurrent TRTx group in both studies.

Alternating vs. Sequential. Inconsistent findings were observed in the 2 studies and no conclusions can be drawn that one is superior to the other. The direction of the advantage on overall survival differed in the 2 studies.

Alternating vs. Concurrent. In the single study comparing alternating and concurrent TRTx, there was no statistically significant effect on survival and no conclusions of differential efficacy could be drawn.

Early Alternating vs. Late Alternating. In the single study comparing early versus late alternating TRTx, there was no statistically significant difference in survival, thus no conclusions of differences in efficacy can be reached.

Key Question 2

For limited-stage SCLC, do outcomes (survival, toxicity, or quality of life) differ if concurrent TRTx is given in early versus late chemotherapy cycles?

Overview

Six randomized, controlled trials (RCTs) compared outcomes of alternate times to administer TRTx concurrently in first-line therapy for limited stage SCLC (N=1,177). Summary Table 10 summarizes selected study variables; further details are in Summary Table 11 and Appendix Tables 2A-C, 2H.* Each of the three larger trials randomized from 125 to 166 patients per arm (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988 [hereafter referred to as "Murray-Coy-Feld"]; Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988; [hereafter referred to as "Perry-Ahles-Perry"]; James, Spiro, O'Donnell, et al., 2003). Together, the three smaller trials

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

included less than one-fourth of all patients studied (Jeremic Shibamoto, Acimovic, et al., 1997; Qiao, Zhou, Xin, et al., 2004; Skarlos, Samantas, Briassoulis, et al., 2001).

Summary Table 10. Selected study parameters of RCTs comparing times to give concurrent TRTx

study	N		Pt?	chemoTx regimen	TRTx dose (Gy)	# fracs	TRTx timing		PCI ?	# centers	pub type	quality rating
	early	late					early	late				
Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988	155	153	yes	CAV/PE	40	1/d	wk 4-6	wk 16-18	yes	multi	full	good
Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988	125	145	no	CAVE	50	1/d	wk 1-5	wk 10-14	yes	multi	full	fair
Jeremic Shibamoto, Acimovic, et al., 1997	52	51	yes	PE/CbE	54	2/d	wk 1-4	wk 6-9	yes	one	full	fair
Qiao, Zhou, Xin, et al., 2004	45	45	yes	CbE	50 or 60	1/d	wk 1-5/6	wk 12-16/17	?	one	full	fair
Skarlos, Samantas, Briassoulis, et al., 2001	42	39	yes	CbE	45	2/d	wk 1-3	wk 10-12	yes	multi	full	fair
James, Spiro, O'Donnell, et al., 2003	159	166	yes	CAV/PE	40	1/d	wk 4-6	wk 16-18	yes	multi	abstr	not rated

Abbreviations table provided at the end of the Report.

Summary Table 11. Sample and Methods: Early Versus Late Radiotherapy

Study	N		Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988 22 centers 1/85 - 12/88	Total	308	md		0 1 2 3		Dose	Schedule	PCI?
	Early	155	61.8	40.6	21.9 65.2 12.3 0.6	CAV-PE	40 Gy	wks 4-6, 1/d, 5/wk, 15/course	25 Gy, 10 frac
	Late	153	61.6	34.6	22.2 68.0 9.2 0.7 ECOG	same	40 Gy	wks 16-18, 1/d, 5/wk, 15/course	same
Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988 22 centers 1/81 - 6/84	Total	270	% < 60		0 1 2/3		Dose	Schedule	PCI?
	Early	125	48	38	38 48 13	CAVE	50 Gy	wks 1-5, 40 Gy+10 Gy boost	30 Gy, 10 frac, con-current with TRTx
	Late	145	45	37	42 45 9 CALGB	same	50 Gy	wks 10-14, 40 Gy+10 Gy boost	
Jeremic Shibamoto, Acimovic, et al., 1997 single center 1/88-12/92	Total	103	mn (rng)		90, 100 50-80		Dose	Schedule	PCI?
	Early	52	57 (40-67)	40.4	52 48	PE/Cb-E	54 Gy	wks 1-4, 2/d, 5/wk	25 Gy, 10 frac, wks
	Late	51	57 (44-66)	39.2	47 53 KPS	same	54 Gy	wks 6-9, 2/d, 5/wk	16, 17

Abbreviations table provided at the end of the Report.

Summary Table 11. Sample and Methods: Early Versus Late Radiotherapy (continued)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Qiao, Zhou, Xin, et al., 2004 single center 3/93-1/98	Total 90 Early 45 Late 45	md (rng) 57 (36-58) 56 (38-69)	 24.3 33.3	all randomized patients had KPS ≥70 (excluded if ≤60)	 Cb-E same	Dose 50-60 Gy 50-60 Gy	Schedule begun 1st CTx cyc, over 6 wks begun after 4th CTx cyc, over 6 wks	PCI? not specified for either arm
Skarlos, Samantas, Briassoulis, et al., 2001 multicenter 12/93 - 11/99	Total 81 Early 42 Late 39	md (rng) 61 (40-76) 60 (37-76)	 7 10	0 1 2 3 26 50 24 41 44 15 ECOG	 Cb-E same	Dose 45 Gy 45 Gy	Schedule wks 1-3, 2/d, 5/wk wks 10-12, 2/d, 5/wk	PCI? 20 Gy, CR 5 4 Gy frac same
James, Spiro, O'Donnell, et al., 2003 (abstract only) multicenter; 1/93 -1/02	Total 325 Early 159 Late 166	md (rng) 62 (34-74) 62 (33-74)	 40 43	0-1 2-3 91 9 89 11 ECOG	 CAV-PE same	Dose 40 Gy 40 Gy	Schedule wks 4-6, 1/d, 5/wk wks 16-18, 1/d, 5/wk	PCI? 25 Gy, 10 frac, neg brain scan

Interventions. Available studies did not uniformly define early and late concurrent therapy, with respect to either the chemotherapy cycle or weeks during which they administered TRTx. Most trials (4 of 6) began TRTx in chemotherapy cycle 1 (i.e., week 1) for those randomized to early concurrent therapy; two waited until cycle 2 (week 4) (Murray-Coy-Feld; James, Spiro, O'Donnell, et al., 2003). Those randomized to late concurrent therapy began TRTx in cycle 3 (week 6) in one trial (Jeremic Shibamoto, Acimovic, et al., 1997), cycle 4 (week 10 or 12) in three trials (Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004; Skarlos, Samantas, Briassoulis, et al., 2001), and cycle 6 (week 16) in the remaining two trials (Murray-Coy-Feld, James, Spiro, O'Donnell, et al., 2003).

Five of six RCTs used platinum-etoposide chemotherapy regimens, including two of three larger trials; Perry-Ahles-Perry was the exception. Total TRTx dose was $\geq$40 Gy in each RCT, and only two used doses greater than 50 Gy (Jeremic Shibamoto, Acimovic, et al., 1997; Qiao, Zhou, Xin, et al., 2004). Three trials gave TRTx over a 3-week period (Murray-Coy-Feld; Skarlos, Samantas, Briassoulis, et al., 2001; James, Spiro, O'Donnell, et al., 2003 2003), one gave TRTx over four weeks (Jeremic Shibamoto, Acimovic, et al., 1997), and two gave TRTX over five or six weeks (Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004). Thus, weekly doses were 10 Gy in two trials (Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004), 13.35 Gy in two trials (Murray-Coy-Feld; James, Spiro, O'Donnell, et al., 2003), and 15 Gy in two trials (Jeremic Shibamoto, Acimovic, et al., 1997; Skarlos, Samantas, Briassoulis, et al., 2001). Four trials administered single daily fractions (Murray-Coy-Feld; Perry-Ahles-Perry; Qiao, Zhou, Xin, et al., 2004; James, Spiro, O'Donnell, et al., 2003) and two gave two fractions per day (Jeremic Shibamoto, Acimovic, et al., 1997; Skarlos, Samantas, Briassoulis, et al., 2001). Five of six trials included PCI for each arm; Qiao, Zhou, Xin, et al. (2004) did not report PCI use.

Study Populations. Most trials studied patients with relatively favorable baseline characteristics, and were nearly always well-balanced across arms for consistently-reported factors (Summary Table 11). In four of six trials, performance status (PS) was 0-1 at enrollment for 75 percent to 91 percent of patients across arms (Murray-Coy-Feld; Perry Ahles-Perry; Skarlos, Samantas, Briassoulis, et al., 2001; James, Spiro, O'Donnell, et al., 2003). PS also was well balanced across arms in Jeremic Shibamoto, Acimovic, et al. (1997), but many patients (~50 percent) had Karnofsky scores of 50-80. Qiao, Zhou, Xin, et al. (2004) excluded patients with Karnofsky PS $\leq$60, but did not report PS distribution by arm. For all six trials, the median or mean age ranged from approximately 55 to 62 years, and was balanced across arms. Each trial enrolled mostly men (8.6 percent women in one trial, 33 percent to 43 percent across five others), and had similar proportions of women in each arm.

Other prognostic factors and baseline characteristics were reported inconsistently (Appendix Table 2B[*]). Only three trials reported the proportion with weight loss at entry (Perry-Ahles-Perry; Jeremic Shibamoto, Acimovic, et al., 1997; Skarlos, Samantas, Briassoulis, et al., 2001). Only three trials reported the proportion with disease outside the lung (Murray-Coy-Feld, Qiao, Zhou, Xin, et al., 2004; Skarlos, Samantas, Briassoulis, et al., 2001). Only one trial reported the proportion of former smokers (Skarlos, Samantas, Briassoulis, et al., 2001). No trials reported racial distributions.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Study Quality and Reporting. The larger studies included one good-quality and one fair-quality multicenter trial, each published in full. The third large trial also was multicenter, but was reported only in abstract and information to rate quality was lacking. Two of three small trials were single-center and one was multicenter; each was of fair quality and published in full.

Results

In one large and two smaller trials, results significantly favored the early TRTx arms for overall (OS), progression-free (PFS), or local recurrence-free (LRFS) survival (Summary Table 12). Murray-Coy-Feld (n=308) reported significantly longer median OS (21.2 versus 16.0 months; p=0.008) and greater 2- and 3-year survival (40 percent versus 33.7 percent and 29.7 percent versus 21.5 percent, respectively) with early TRTx. Murray-Coy-Feld also reported significantly greater PFS with early TRTx (median, 15.4 versus 11.8 months; 26 percent versus 19 percent at 3 years; p=0.036). Qiao, Zhou, Xin, et al. (2004; n=90) reported longer median OS (26 versus 19 months; p<0.05) and greater 3-year survival (33 percent versus 22 percent) with early TRTx, but did not report an outcome related to progression or recurrence. Jeremic Shibamoto, Acimovic, et al. (1997; n=103) reported significantly greater 2- and 3-year LRFS with early TRTx (90 percent versus 69 percent and 73 percent versus 61 percent, respectively; p=0.011). While median OS (34 versus 26 months) and 2- and 3-year survival also favored early TRTx in the Jeremic Shibamoto, Acimovic, et al. (1997) trial, these results were just barely statistically nonsignificant (p=0.052).

Between-arm differences in response rates were not statistically significant in any trial (Appendix Table 2F).

In two large and one smaller RCTs, OS and time to treatment failure (TTF) did not differ significantly between arms randomized to early or late TRTx (Summary Table 12). Perry-Ahles-Perry (n=270), the only trial that did not use platinum, reported non-significant differences in OS (P=0.144) and TTF (p=0.238). James, Spiro, O'Donnell, et al. (2003; n=325), the sole trial published as an abstract, only reported OS and also found no significant difference (p=0.18). Skarlos, Samantas, Briassoulis, et al. (2001; n=81) reported nonsignificant differences for median OS (p=0.65) and median TTF (p=0.6).

A small pilot sub-study from one RCT reported the only data comparing quality of life outcomes after early versus late TRTx. Ahles et al. (1994) scored responses to measures of mood, psychosocial function, and cognitive function for 14-17 patients (of n=121) given early TRTx and 10-12 (of n=141) given late TRTx in the Perry-Ahles-Perry trial (Appendix Table 2F).[*]

Summary Table 12. Survival Outcomes: Early Versus Late Radiotherapy

Study	N	Overall Survival Med	1 yr	2 yr	3 yr	4 yr	5 yr	Other Outcomes (progression, failure, relapse, etc.) Med	1 yr	2 yr	3 yr	4 yr	5 yr
Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988	Early 155	21.2	~77%	40%	29.7%	23.7%	20%	15.4	~65%	~28%	26%		
	Late 153	16.0	~63%	33.7%	21.5%	15.1%	11%	11.8	~48%	~24%	19%		
	Difference	5.2	14%	6.3%	8.2%	8.6%	9%	3.6	17%	4%	7%		
		(p=0.008, log-rank; 0.005 Wilcoxon)						(PFS, p=0.036, log-rank; 0.014 Wilcoxon)					
Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988	Early 125	13.0	~53%	~24%	~10%			11.0	~45%	15%	~8%		
	Late 145	14.5	~62%	~30%	~20%			11.2	~50%	25%	~15%		
	Difference	-1.5	-9%	-6%	-10%			-0.2	-5%	-10%	-7%		
		(p=0.144; not significant)						(TTF, p=0.238; not significant)					
Jeremic Shibamoto, Acimovic, et al., 1997	Early 52	34	90%	71%	48%	35%	30%	52	94%	90%	73%	63%	58%
	Late 51	26	71%	53%	39%	25%	15%	51	74%	69%	61%	46%	37%
	Difference	8	19%	18%	9%	10%	15%	1	20%	21%	12%	17%	21%
		(p=0.052)						(LRFS, p=0.011)					
Qiao, Zhou, Xin, et al., 2004	Early 45	26	78%		33%		27%						
	Late 45	19	53%		22%		16%						
	Difference	7	25%		11%		11%						
		(log-rank, p<0.05)											
Skarlos, Samantas, Briassoulis, et al., 2001	Early 42	17.5	~65%	36%	22%			9.5	~40%	~25%	~20%		
	Late 39	17	~80%	29%	13%			10.5	~35%	~15%	~15%		
	Difference	0.5	-15%	7%	9%			-1.0	5%	10%	5%		
		(p=0.65, not significant)						(TTF, p=0.6, not significant)					
James, Spiro, O'Donnell, et al., 2003 (abstract only)	Early 159	13.5			16%								
	Late 166	15.1			20%								
	Difference	-1.6			-4%								
		(HR = 1.18; 95% CI: 0.93, 1.51; p=0.18)											

Abbreviations table available at the end of the Report.

They compared these with scores for another group randomized to chemotherapy without TRTx (not abstracted). Results suggested larger decrements of mood and psychosocial function after chemotherapy plus TRTx than after chemotherapy alone. However, they found no meaningful differences in magnitude of decrement between early and late TRTx groups.

Table 13 shows that leukopenia/neutropenia and esophagitis were the only adverse events consistently reported by all six trials. Although leukopenia/neutropenia was more common in the early arm of five RCTs, only Qiao, Zhou, Xin, et al. (2004; $p<0.05$) and James, Spiro, O'Donnell, et al. (2003; $p=0.006$) reported that differences were statistically significant (Summary Table 14). Of four reporting RCTs, only Murray-Coy-Feld reported significantly more anemia in the early treatment arm (49 percent versus 37 percent, $p=0.03$). Skarlos, Samantas, Briassoulis, et al. (2001) reported significantly more grade 3 esophagitis with late than with early TRTx. However, the arms did not differ significantly when grades 1-3 were pooled, and the other five trials reported no significant differences in grade 3 or 3+4 combined.

Summary Table 13. Adverse Events, Early versus Late Concurrent TRTx

Adverse Event	Murray/Coy/ Feld	Perry/Ahles/ Perry	Jeremic 1997	Qiao 2004	Skarlos 2001	James 2003
leukopenia/ neutropenia				▲		▲
anemia	▲	NR		NR		
esophagitis					▼	

▲=significantly more frequent in early than in late arm; ▼=significantly less frequent in early than in late arm; NR=not reported; blank cell=outcome reported, but arms not significantly different

Between-arm differences in treatment-related mortality (3 reporting trials), nausea/ vomiting (5 reporting trials), neurosensory effects (3 reporting trials), bronchopulmonary effects or pneumonitis (3 reporting trials each), thrombocytopenia (5 reporting trials), and infections (4 reporting trials) were not statistically significant.

Conclusions

Overall, the evidence is equivocal, either finding no difference or a small advantage for early TRTx. One larger trial of good quality significantly favored concurrent therapy given in an early cycle (Murray-Coy-Feld; median OS 21.2 versus 16.0 months; $p=0.008$), as did 2 smaller trials. Of the two larger trials that that found no significant difference, one did not use platinum chemotherapy and the other has not been published in full text. Meta-analysis on the question of early versus late TRTx was performed to attempt to obtain clearer results.

Leukopenia/neutropenia appeared to be more common with early concurrent TRTx, although differences were statistically significant in only two of six reporting trials. Other events do not appear to be more frequent with either early or late TRTx. However, evidence is limited as adverse events were not reported consistently across all trials.

S`1ummary Table 14. Adverse Events: Early Versus Late Radiotherapy

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Treatment-related mortality	Murray 1993 Coy 1994 Feld 1988		155	1.3	153	1.3	NS	Jeremic 1997; Qiao 2004; James 2003
	Perry 1987 Ahles 1994 Perry 1998		125	4	145	1	NS	
	Skarlos 2001		42	0	39	0	NS	
Nausea/Vomiting	Murray 1993 Coy 1994 Feld 1988	required IV fluids	155	11.6	153	15.8	NS	Qiao 2004
	Perry 1987 Ahles 1994 Perry 1998	nausea and vomiting, NOS	122	18	140	10	NS	
	Jeremic 1997	nausea and vomiting, grades 3 & 4	52	9.6	51	7.8	NS	
	Skarlos 2001	grade 3 nausea and vomiting	42	2.5	39	2.5	NS	
	James 2003	nausea and vomiting, grades 3 & 4	159	2	166	3	NS	
Anorexia	Perry 1987 Ahles 1994 Perry 1998	>10% weight loss	?	14	NR	NR		Murray 1993/Coy 1994/Feld 1988; Jeremic 1997; Skarlos 2001; James, 2003
	Qiao 2004	weight loss (% not specified)	45	20	45	33.3	NS	
Lethargy								Murray 1993/Coy 1994/Feld 1988; Perry 1987/Ahles 1994/Perry 1998; Jeremic 1997; Qiao 2004; Skarlos 2001; James, 2003
Neurosensory	Murray 1993 Coy 1994 Feld 1988	severe life-threatening lethal	155	0.6 0 0.6	153	3.3 1.3 0	NS for all 3 levels combined	Jeremic 1997; Qiao 2004; James, 2003
	Perry 1987 Ahles 1994 Perry 1998	“neuromuscular effects”	124	17	144	16	NS	
	Skarlos 2001	grade 2 & 3 neurotoxicity	42	0	39	0	NS	
Hearing loss								Murray 1993/Coy 1994/Feld 1988; Perry 1987/Ahles 1994/Perry 1998; Jeremic 1997; Qiao 2004; Skarlos 2001; James, 2003

Abbreviations table provided at the end of the Report.

Summary Table 14. Adverse Events: Early Versus Late Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Esophagitis	Murray 1993 Coy 1994 Feld 1988	fluids only IV fluids	149	11.4 3.4	133	6.8 0.8	NS for both levels combined	
	Perry 1987 Ahles 1994 Perry 1998	not specified	?	10	?	8		
	Jeremic 1997	grades 3 & 4	52	28.9	51	25.5	NS	
	Qiao 2004		45	42.2	45	28.9	NS	
	Skarlos 2001	grade 3	42	2.5	39	18	0.026 (p=0.82 for overall incidence)	
	James 2003	grades 3 & 4	159	7	166	4	NS	
Bronchopulmonary	Perry 1987 Ahles 1994 Perry 1998	not specified	122	9	133	6	NS	Murray 1993/Coy 1994/Feld 1988; Qiao 2004; James 2003
	Jeremic 1997	grades 3 & 4	52	1.9	51	0	NS	
	Skarlos 2001	Grade 3	42	5.0	39	7.5	NS	
Pneumonitis	Murray 1993 Coy 1994 Feld 1988	any lethal	149	3.2 0	133	0.7 0	NS	Jeremic 1997; Skarlos 2001; James, 2003
	Perry 1987 Ahles 1994 Perry 1998	not specified	122	9	133	4.5	NS	
	Qiao 2004	radio-pneumonia	45	8.9	45	6.7	NS	
Kidney	Murray 1993 Coy 1994 Feld 1988	creatinine > 354 μmol/L	155	0	153	0.7	NS	Perry 1987/Ahles 1994/Perry 1998; Jeremic 1997; Qiao 2004; James, 2003
	Skarlos 2001	grade 2 or 3	42	0	39	0	NS	
Anemia	Murray 1993 Coy 1994 Feld 1988	Hb <80 g/L	155	49	153	36.8	0.0275	Perry 1987/Ahles 1994/Perry 1998; Qiao 2004
	Jeremic 1997	grades 3 & 4	52	13.5	51	7.8	NS	
	Skarlos 2001	grades 3 & 4	42	19	39	12.5	NS	
	James, 2003	grades 3 & 4	159	9	166	5	NS	
Thrombocytopenia	Murray 1993 Coy 1994 Feld 1988	$<25 \times 10^9$/L	155	3.9	153	2.6	NS	Qiao 2004
	Perry 1987 Ahles 1994 Perry 1998	$<25 \times 10^9$/L	122	1	140	2	NS	
	Jeremic 1997	grades 3 & 4	52	38.5	51	21.6	NS	
	Skarlos 2001	grades 3 & 4	42	21.5	39	23	NS	
	James, 2003	grades 3 & 4	159	9	166	9	NS	

Summary Table 14. Adverse Events: Early Versus Late Radiotherapy (continued)

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Leukopenia or neutropenia	Murray 1993 Coy 1994 Feld 1988	neutrophils<0.5 x 10^9/L	155	70.3	153	61.4	NS	
	Perry 1987 Ahles 1994 Perry 1998	WBC<1 x 10^9/L	117	35	118	25	NS	
	Jeremic 1997	leukopenia, grades 3 & 4	52	32.7	51	41.2	NS	
	Qiao 2004	grade 2 grade 3 grade 4	45	6.7 71.1 22.2	45	24.4 57.8 17.8	 0.02 (for 3+4)	
	Skarlos 2001	grades 3 & 4 leukopenia	42	35.5	39	20.5	NS	
	James, 2003	grades 3-4 leucopenia	159	74	166	55	0.006	
Infection	Murray 1993 Coy 1994 Feld 1988	neutropenic fever septic shock lethal	155	4.5 0.6 0	153	3.3 0.7 1.3	NS (for all 3 combined)	Qiao 2004; James, 2003
	Perry 1987 Ahles 1994 Perry 1998	sepsis	125	20	140	15	NS	
	Jeremeic 1997	grades 3 & 4	52	13.5	51	13.7	NS	
	Skarlos 2001	neutropenic fever	42	5	39	2.5	NS	
Other	Murray 1993 Coy 1994 Feld 1988	severe dermatitis blisters	149	2.0 4.0	133	1.5 0.7	NS (for both combined)	
	Qiao 2004	mild digestive tract reaction	45	73.3	45	55.6	NS	

Meta-Analysis/Meta-Regression

Overview

All but one of the studies selected for Key Questions 1 and 2 can be viewed as comparing early and late TRTx. Key Question 2 is limited to studies in which both early and late TRTx were given concurrently with chemotherapy, while Key Question 1 included those with arms defined by TRTx given either concurrently, sequentially or in alternating fashion. Only the study by Lebeau, Urban, Brechot et al. (1999) is excluded because only 1 week separated the start of TRTx in the study's 2 arms. Four previous meta-analyses have compared the impact of early and late TRTx, but none have included all 11 studies reviewed here. Three meta-analyses are summarized in Summary Table 25; a meta-analysis by Cancer Care Ontario (2003) is omitted because it used much more restrictive study selection criteria, including only 4 studies. The meta-analysis of 8 studies by Fried, Morris, Poole, et al. (2004) used the most rigorous methods and comprised the largest pool of the previous meta-analyses. The present meta-analysis addresses whether the findings of Fried, Morris, Poole, et al. (2004) can be reproduced in light of a larger study pool and different meta-analytic techniques.

Fried, Morris, Poole, et al. (2004) used the Mantel-Haenszel pooling method and found no significant heterogeneity at either 2 or 3 years; thus, fixed-effects models were employed. A significant increase in 2-year survival was found for early TRTx over late TRTx (RR: 1.17, 95 percent CI: 1.02–1.35). The effect was not significant at 3 years (RR: 1.13, 95 percent CI: 0.92–1.39). Subgroups of studies using hyperfractionation and platinum regimens had significant increases in 2- and 3-year survival favoring early TRTx, nonsignificant results were found for subgroups that did not use hyperfraction and platinum. Random effects meta-regression of risk differences (RDs) found that higher RDs were seen at both 2 and 3 years when studies used both hyperfractionation and platinum chemotherapy. Thus, larger effects of early over late TRTx were associated with combining hyperfractionation and platinum chemotherapy.

The present meta-analysis differs from that of Fried, Morris, Poole, et al. (2004) in the following ways: it included 3 additional studies; it used inverse variance weighting rather than the Mantel-Haenszel pooling method; and random effects meta-regression was carried out using RRs for this analysis and RDs by Fried, Morris, Poole, et al. (2004). In addition, Fried, Morris, Poole, et al. (2004) created 3 subgroups from the combination of hyperfractionation and platinum and used indicator variables for them in the meta-regression. This Review kept these variables separate. It could be argued that the hetereogeneity of comparisons across studies is too great to warrant pooling them. Like previous meta-analyses on this topic, we address this concern by using influence analysis, subgroup/sensitivity analysis, and meta-regression to investigate whether potential sources of hetereogeneity are associated with different results.

2-Year Mortality. The funnel plot in Figure 2 shows asymmetry in the lower right portion, suggestive of publication bias. The Egger regression test (Summary Table 15) reveals that the intercept differs significantly from zero. These results suggest the presence of publication bias.

Summary Table 16 and Figure 3 show 2-year RRs for each individual trial, along with 95 percent confidence intervals (CIs). It should be noted that all RRs were computed based on data from articles for all studies except Park, Kim, Jeong, et al. (1996). The Park, Kim, Jeong, et al. (1996) article did not give survival probabilities at yearly periods so an author was contacted

who provided data for a larger sample than was described in the original articles. The Sun, Zhang, Yin, et al. (1995) and Takada, Fukuoka, Kawahara, et al. (2002) trials both obtained 2-year RRs showing a significant reduction in the risk of mortality for early TRTx. One study (Perry, Herndon, Eaton, et al. 1998) found a slight nonsignificant increase in mortality for early TRTx and the remaining 6 studies yielded nonsignificant decreases in mortality for early TRTx.

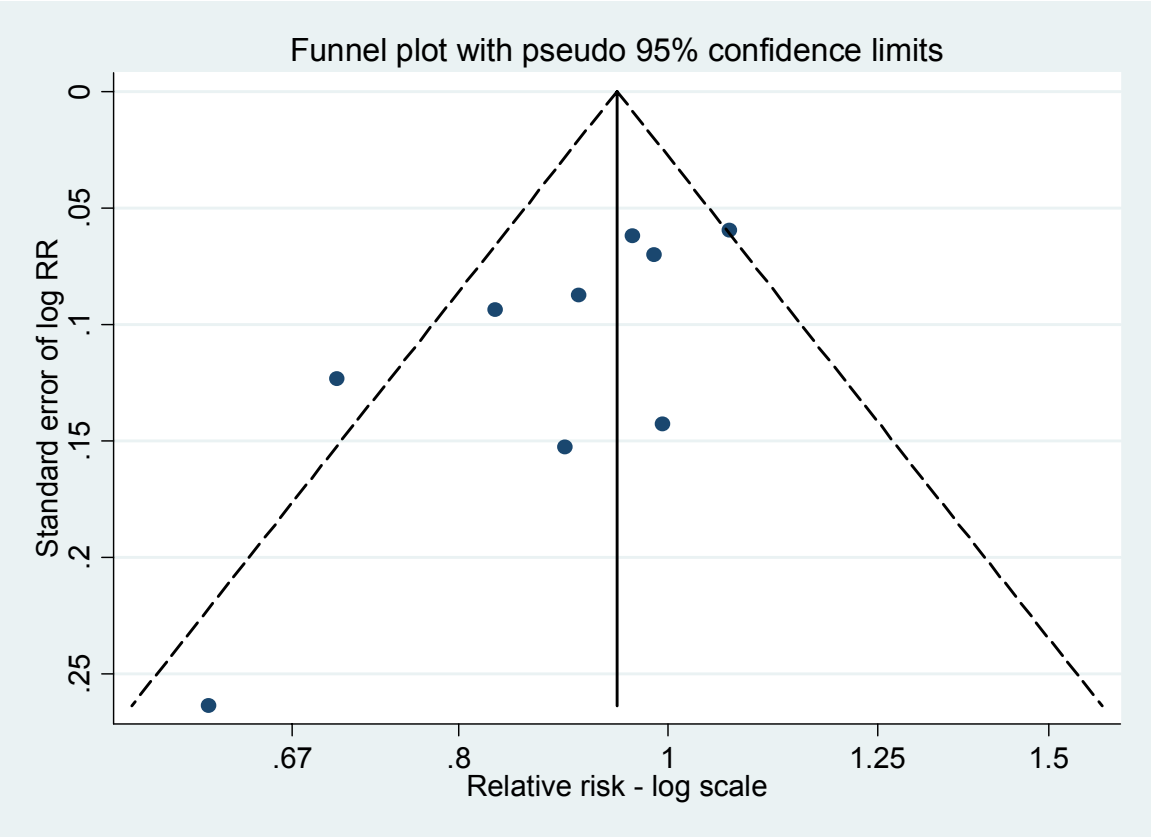


Figure 2: Two-Year Mortality Funnel Plot, Early vs.Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 15. Egger Linear Regression Test for Publication Bias, 2-Year Mortality

	Coefficient	Standard Error	L95	U95	t	p value
Intercept	-2.444	0.936	-4.658	-0.230	-2.61	0.035

Summary Table 16. Individual Trial 2-Year Mortality Relative Risks, Confidence Intervals and Covariate Matrix

Study	Early Deaths	Early n	Late Deaths	Late n	RR	L95	U95	Earliest	Hyper	Plat	Conc	GQ
Murray	93	155	101	153	0.909	0.766	1.079	0	0	1	1	1
Sun	46	64	51	59	0.831	0.692	0.999	0	0	0	0	0
Park	23	32	34	47	0.994	0.751	1.314	1	1	1	0	0
Gregor	126	170	127	165	0.963	0.852	1.088	0	0	0	0	1
Jeremic	15	52	24	51	0.613	0.366	1.028	1	1	1	1	0
Work	79	99	81	100	0.985	0.859	1.130	1	0	1	0	0
Perry	104	125	113	145	1.068	0.950	1.200	1	0	0	1	0
Skarlos	27	42	28	39	0.895	0.664	1.208	1	1	1	1	0
Takada	52	114	74	114	0.703	0.552	0.895	1	1	1	0	1

The Q statistic value obtained here (Summary Table 17) exceeds the threshold for concluding that significant heterogeneity of treatment effects exists, therefore a random effects pooled estimate was computed (see forest plot in Figure 3). The pooled RR is 0.921 and the 95 percent CI overlaps the null value of 1.0 (0.844, 1.005). Figure 4 presents the results of influence analysis, in which each individual study is excluded from the random effects pooled estimate. This graph can be interpreted by finding the studies that depart to the greatest extent from the vertical line for the full pooled estimate RR of 0.92. When the Perry study is excluded, the lowest RR estimate, 0.898, is obtained. So Perry exerts the greatest influence of pulling the pooled estimate toward the null or an advantage for late TRTx. Exclusion of the Takada, Fukuoka, Kawahara, et al. (2002) study results in the highest RR estimate, 0.955. Takada, Fukuoka, Kawahara, et al. (2002) is the most influential study in drawing the pooled estimate in the direction favoring early TRTx. Exclusion of the Perry study was the only instance in which a significant pooled result was obtained. However, as a whole, excluding any individual study has little influence on the estimate of the pooled RR.

Summary Table 17. Results from Heterogeneity Tests and Random Effects Meta-Analysis

	Study n	Subject n	Q	p value	RE RR	L95	U95	Z	p Value
2-Year Mortality	9	1726	15.393	0.052	0.921	0.844	1.005	-1.852	0.064

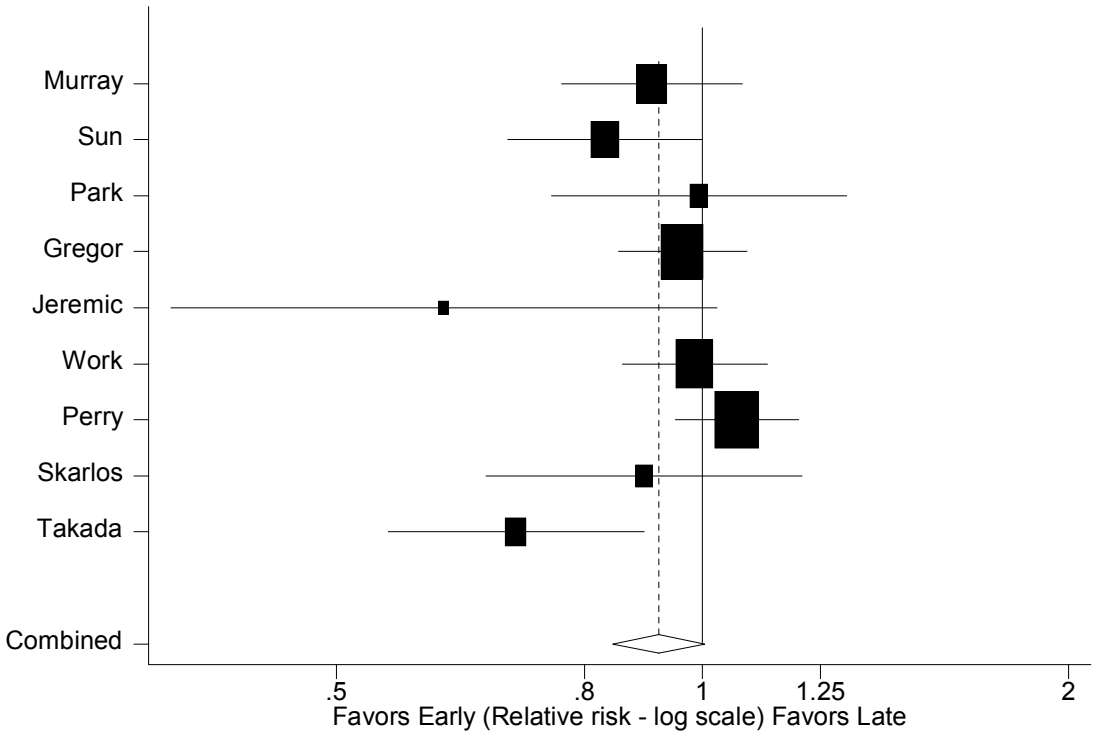


Figure 3: Two-Year Mortality Random Effects Forest Plot, Early vs.Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer, All Trials

Summary Table 18 gives the results of subgroup/sensitivity analysis. Selection of variables defining subgroups was constrained by the relatively small pool of studies. Fine gradations of variables dilute the power to detect differences between early and late TRTx. Two concerns guide interpretation of subgroup results: the magnitude of differences in RR point estimates for different levels of a variable and whether statistical significance is achieved in any subgroup. Q statistic values exceeded the threshold for significant heterogeneity in 4 instances: among those studies that delivered the early TRTx at the earliest time (beginning in the first week of chemotherapy), those that did not use platinum chemotherapy, those that gave TRTx and chemotherapy concurrently, and those studies rated as being of good quality. These subgroups were pooled using random-effects models, while all other subgroups were pooled with fixed-effects.

Use of hyperfractionation was the variable with the greatest difference in point estimates of RR between subgroups of studies. Inclusion of studies using hyperfractionation produced a significant pooled RR of 0.815 (95 percent CI: 0.702–0.946). Studies that used once daily fractionation had a pooled RR much closer to the null, 0.972 (95 percent CI: 0.913–1.035). There was a moderate difference between point estimates of those studies that did and did not use platinum. Studies using platinum in chemotherapy regimens obtained a greater reduction in mortality, with a significant RR of 0.905 (95 percent CI: 0.829–0.987). Those not using

platinum yielded an RR close to the null, 0.964 (95 percent CI: 0.848–1.096). The set of studies that offered the earliest early TRTx did not result in a statistically significant reduction in mortality at 2 years for early TRTx (RR=0.914, 95 percent CI: 0.792–1.054). The point estimate for those studies not among the earliest was nearly identical and also nonsignificant (RR=0.918, 95 percent CI: 0.841–1.001). .Those using concurrent TRTx had a nonsignificant RR of 0.938 (95 percent CI: 0.799–1.100) and those not using concurrent TRTx had a significant RR of 0.920 (95 percent CI: 0.854–0.992). There was a considerable difference between studies of good quality and lesser quality, but pooled results were nonsignificant for both. Good quality studies produced a RR of 0.874 (95 percent CI: 0.744–1.027). Lesser quality studies had a RR of 0.975 (95 CI: 0.906–1.050). A random effects meta-regression (Table 19) found that no variables was a significant predict of differences in treatment effect at 2 years, but hyperfractionation was nearly significant (p=0.07).

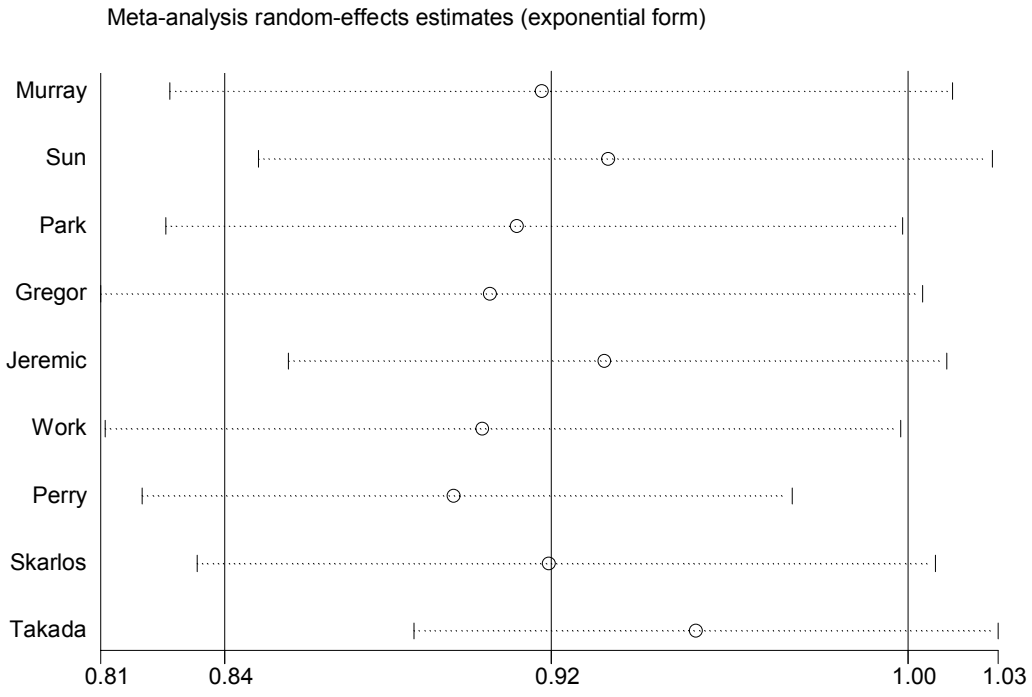


Figure 4: Two-Year Mortality Random Effects Influence Plot, Early vs.Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 18. Results of Subgroup/Sensitivity Analyses, Two-Year Mortality

2-Year Mortality	Study n	Subject n	Q	p value	Model	RR	L95	U95	Z	p value
Earliest-Yes	6	960	12.796	0.025	RE	0.914	0.792	1.054	-1.241	0.215
Earliest-No	3	766	1.720	0.423	FE	0.918	0.841	1.001	-1.929	0.054
Hyperfractionation-Yes	4	491	4.921	0.178	FE	0.815	0.702	0.946	-2.691	0.007
Hyperfractionation-No	5	1235	5.893	0.207	FE	0.972	0.913	1.035	-0.890	0.373
Platinum-Yes	6	998	8.300	0.140	FE	0.905	0.829	0.987	-2.258	0.024
Platinum-No	3	728	5.212	0.074	RE	0.964	0.848	1.096	-0.563	0.573
Concurrent RTx-Yes	4	762	6.285	0.099	RE	0.938	0.799	1.100	-0.790	0.430
Concurrent RTx-No	5	964	7.726	0.102	FE	0.920	0.854	0.992	-2.182	0.029
Good Quality-Yes	3	871	5.209	0.074	RE	0.874	0.744	1.027	-1.638	0.101
Good Quality-No	6	855	8.647	0.124	FE	0.975	0.906	1.050	-0.672	0.501

Summary Table 19. Results of Meta-Regression

2 Year Mortality

Model	Z	p value	Initial tau squared	Model tau squared
Earliest	0.26	0.797	0.0077	0.0086
Hyperfractionation	-1.81	0.070		0.0034
Platinum	-0.98	0.327		0.0070
Concurrent	0.57	0.571		0.0074
Good Quality	-0.82	0.414		0.0073

3-Year Mortality. The funnel plot (Figure 5) suggests the presence of publication bias. Point estimates appear to be missing in the lower right region of the plot. Linear regression (Egger test, Table 20) shows that the intercept differs significantly from zero, confirming that publication bias may be present.

Three-year mortality RRs for individual trials are given in Table 21. Three trials obtained RR estimates favoring late TRTx, while the other 8 favor early TRTx. The 95 percent CIs all overlap the null value RR of 1.0.

Table 22 shows that the Q statistic value does not exceed the level for concluding that significant heterogeneity of effects is present. Thus, a fixed effects model was used to compute a pooled 3-year RR (see forest plot in Figure 6). The obtained estimate was 0.991 (95 percent CI: 0.955–1.029). Based on these results, it cannot be concluded that use of early TRTx significant reduces the risk of mortality at 3 years.

The influence analysis plot in Figure 7 shows only extremely small changes in the pooled RR estimate when individual studies are excluded. When the Perry study is excluded, the lowest pooled RR estimate is produced: 0.977. This study has the greatest impact on drawing the pooled RR toward the null or effects favoring late TRTx. The largest pooled RR is derived when the Murray study is excluded: 1.000. Murray has the strongest influence on pulling the pooled RR away from the null, favoring early TRTx. Point estimates changed very little when individual studies were excluded.

Results of subgroup/sensitivity analysis are presented in Summary Table 23. The subset of studies using hyperfractionation yielded a significant pooled RR of 0.908 (95 percent CI: 0.828–0.995). Those that used once daily fractionation had a nonsignificant pooled RR of 1.008 (95 percent CI: 0.968–1.050). No other subgroup produced a significant result. Studies in which platinum was part of chemotherapy regimens had an RR of 0.958 (95 percent CI: 0.910–1.009). Non-platinum studies produced an RR of 1.029 (95 percent CI: 0.975–1.085). The group of studies in which early TRTx was begun at the earliest time produced a nearly null-value RR (0.998, 95 percent CI: 0.953–1.045). Those studies that began early TRTx after the first week of chemotherapy produced a similar RR (0.980, 95 percent CI: 0.921–1.042). Studies that offered concurrent RTx had a similar pooled RR (0.997, 95 percent CI: 0.947–1.051) compared with

those that did not (RR: 0.985, 95 percent CI: 0.935–1.038). There was a modest difference between studies of good quality versus lesser quality. Good quality studies had an RR of 0.948 (95 percent CI: 0.843–1.064), while fair and poor quality studies had an RR of 1.000 (95 CI: 0.956, 1.047). Results of random effects meta-regression are shown in Summary Table 24. Use of hyperfractionation (p=0.04) was the only significant predictor, while use of platinum (p=0.06) was nearly a significant predictor of differences in treatment effects.

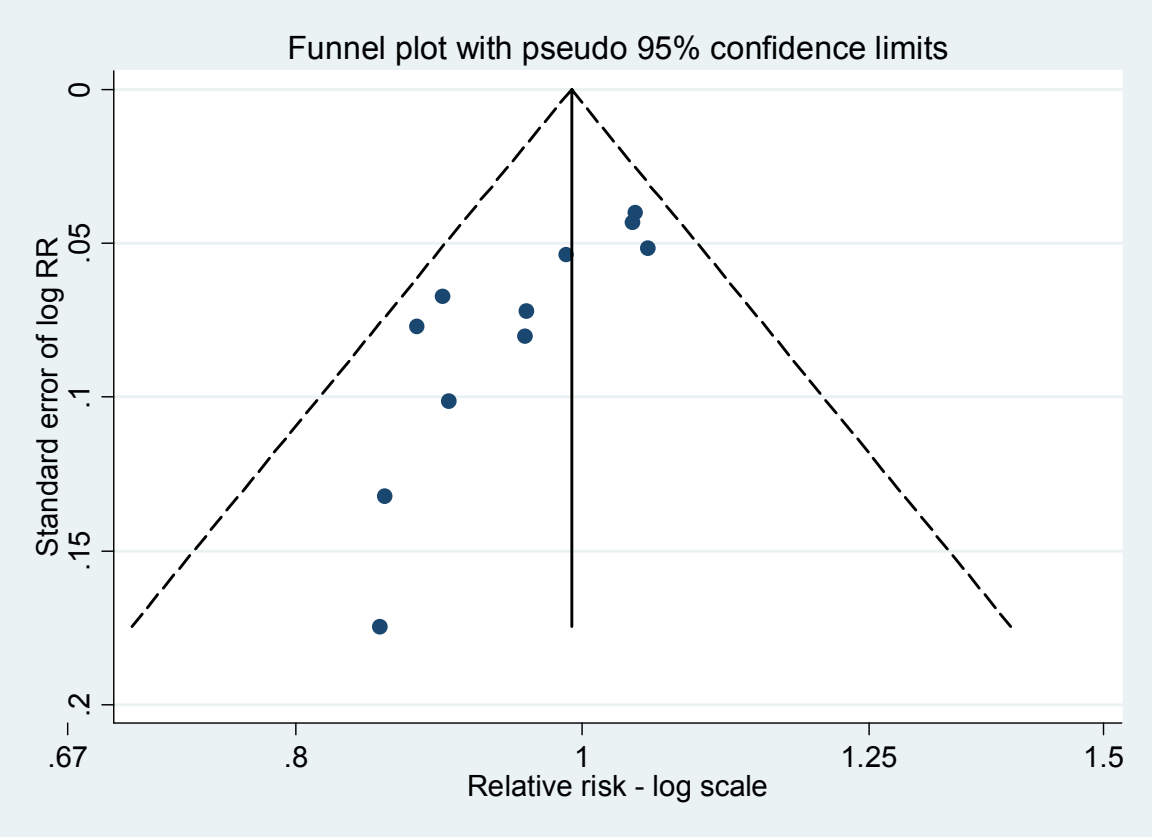


Figure 5: Three-Year Mortality Funnel Plot, Early vs. Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 20. Egger Linear Regression Test for Publication Bias, 3Year Mortality

	Coefficient	Standard Error	L95	U95	t	p value
Intercept	-2.351	0.540	-3.573	-1.130	-4.35	0.002

Summary Table 21. Individual Trial 3-Year Mortality Relative Risks, Confidence Intervals and Covariate Matrix

Study	Early Deaths	Early N	Late Deaths	Late n	RR	L95	U95	Earliest	Hyper	Plat	Conc	GQ
Murray	109	155	120	153	0.897	0.786	1.023	0	0	1	1	1
Sun	54	64	52	59	0.957	0.831	1.102	0	0	0	0	0
Park	28	32	43	47	0.956	0.817	1.119	1	1	1	0	0
Gregor	150	170	140	165	1.040	0.955	1.132	0	0	0	0	1
Jeremic	27	52	31	51	0.854	0.607	1.203	1	1	1	1	0
Work	86	99	88	100	0.987	0.888	1.097	1	0	1	0	0
Perry	115	125	128	145	1.042	0.963	1.128	1	0	0	1	0
Skarlos	33	42	34	39	0.901	0.739	1.099	1	1	1	1	0
Takada	80	114	91	114	0.879	0.756	1.023	1	1	1	0	1
James	134	159	133	166	1.052	0.951	1.164	1	0	1	1	0
Qiao	30	45	35	45	0.857	0.662	1.111	0	0	1	1	0

Summary Table 22. Results from Heterogeneity Tests and Fixed Effects Meta-Analysis

	Study n	Subject n	Q	p value	FE RR	L95	U95	Z	p Value
3-Year Mortality	11	2141	12.019	0.284	0.991	0.955	1.029	-0.457	0.648

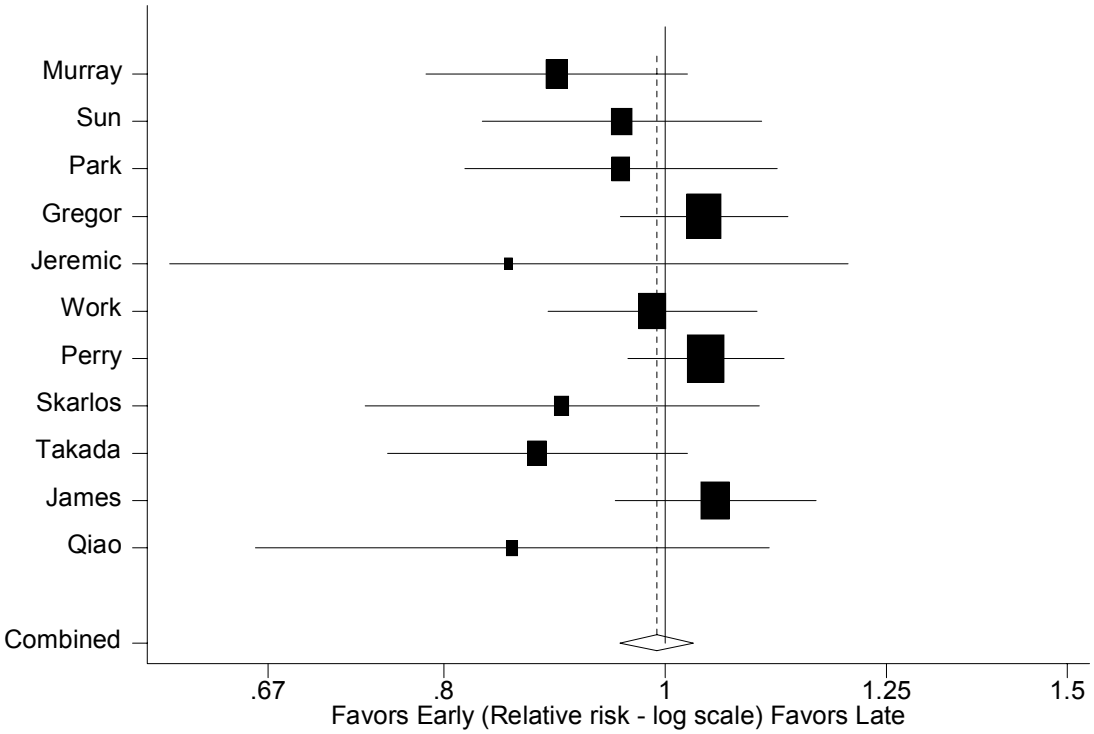


Figure 6: Three-Year Mortality Fixed Effects Forest Plot, Early vs. Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer, All Trials

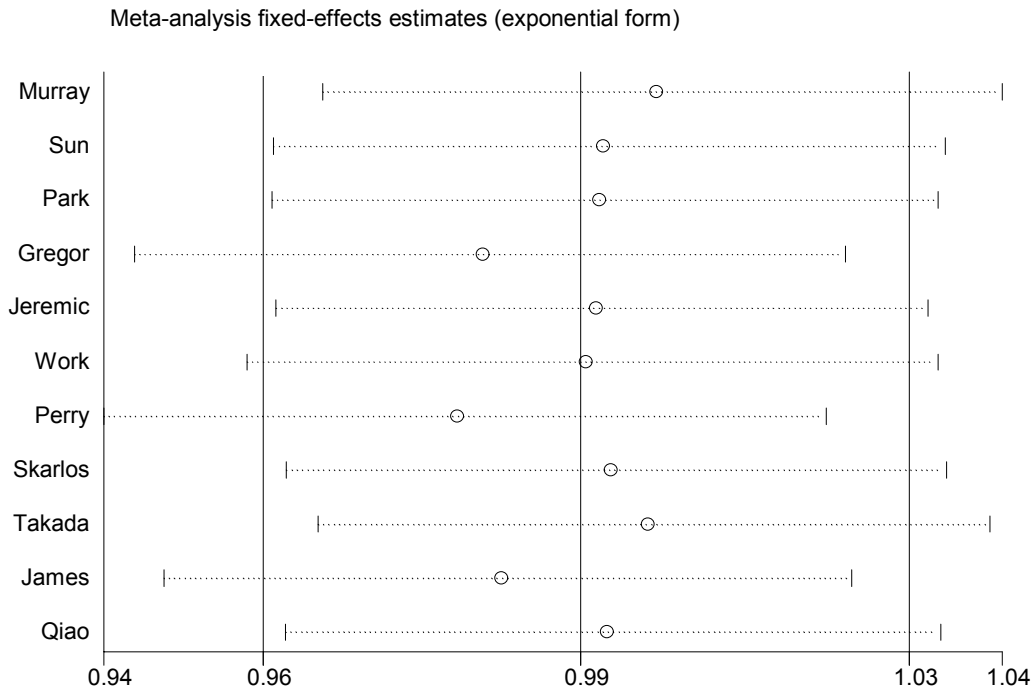


Figure 7: Three-Year Mortality Fixed Effects Influence Plot, Early vs. Late Thoracic Radiotherapy for Limited Stage Small-Cell Lung Cancer

Summary Table 23. Results of Subgroup/Sensitivity Analyses, Three-Year Mortality

3-Year Mortality	Study n	Subject n	Q	p value	Model	RR	L95	U95	Z	p value
Earliest-Yes	7	1285	7.037	0.317	FE	0.998	0.953	1.045	-0.089	0.929
Earliest-No	4	856	4.770	0.189	FE	0.980	0.921	1.042	-0.644	0.520
Hyperfractionation-Yes	4	491	0.722	0.868	FE	0.908	0.828	0.995	-2.061	0.039
Hyperfractionation-No	7	1650	7.095	0.312	FE	1.008	0.968	1.050	0.406	0.685
Platinum-Yes	8	1413	7.302	0.398	FE	0.958	0.910	1.009	-1.637	0.102
Platinum-No	3	728	1.167	0.558	FE	1.029	0.975	1.085	1.039	0.299
Concurrent RTx-Yes	6	1177	7.872	0.163	FE	0.997	0.947	1.051	-0.098	0.922
Concurrent RTx-No	5	964	4.045	0.400	FE	0.985	0.935	1.038	-0.549	0.583
Good Quality-Yes	3	871	5.580	0.061	RE	0.948	0.843	1.064	-0.908	0.364
Good Quality-No	8	1270	5.981	0.542	FE	1.000	0.956	1.047	0.015	0.988

Summary Table 24. Results of Meta-Regression

3 Year Mortality

Model	Z	p value	Initial tau squared	Model tau squared
Earliest	0.40	0.688	0.0008	0.0016
Hyperfractionation	-2.05	0.040		<0.0001
Platinum	-1.88	0.060		<0.0001
Concurrent	0.12	0.906		0.0016
Good Quality	-0.61	0.540		0.0015

Summary Table 25. Summary of Published Meta-Analyses on Early Versus Late Thoracic Radiation Therapy for Limited-Stage Small-Cell Lung Cancer

Study/ Meta-Analysis	Takada 2002	Murray 1993	Perry 1998	Jeremic 1997	Skarlos 2001	Work 1997	James 2003	Gregor 1997	Lebeau 1999	Goto 1999	Sun 1995	Qiao 2004	Park 1996	Method/ Measures	Handling of Hetero-geneity	Results(ratios compare early to late)
Fried, Morris, Poole, et al. (2004)	X	X	X	X	X	X	*	X						Fixed effects (M-H) 2 yr OS 3 yr OS RR RD NNT	M-H χ^2, subgroup analysis, sensitivity analysis, random effects meta-regression	All studies: 2 yr: OS RR 1.17 (1.02, 1.35); 3 yr OS RR 1.13 (0.92, 1.39) M-H χ^2 p=.17, 2 yr, p=.18, 3 yr Excluding Takada had large impact Subgroups: 2 yr p 3 yr p Hyperfractionation Y .001 .04 N NS NS Platinum Y .002 .01 N NS NS Concurrent RTx Y NS NS N NS NS M-R: hyperfractionation, platinum predicted significant difference between RDs
Pijls-Johannesma , De Ruysscher, Lambin, et al. (2005)	X	X	X	X	X	X	X							Random effects 2-3 yr OS 5 yr OS OR, RR	χ^2, subgroup analysis, random effects meta-regression	All studies: 2-3 yr OS OR: 0.84 (0.56, 1.28); 5 yr OS OR 0.80 (0.47, 1.38) χ^2 p=.006, 2-3 yr; p=05, 5 yr Subgroups: 2-3 yr p 5 yr p Platinum Y .01 .01 N .02 NS RTx < 30 d Y NS .006 M-R: significant association between RTx < 30 d and survival, 5 yr
Huncharek & McGarry (2004)	X	X	X	X	X	X			X	X				Fixed effects (Peto) 1 yr OS 2 yr OS 3 yr OS Peto OR	Q, sensitivity analysis	All studies: 1 yr OS P-OR: 1.11 (0.88, 1.40); 2 yr OS P-OR: 1.60 (1.29, 1.99); 3 yr OS P-OR: 1.49 (1.15, 1.93) Q, p<.001, 1 yr; p=.24, 2 yr; p=.81, 3 yr Subgroups: 1 yr p 2 yr p 3 yr p -Work, -Lebeau <.05<.05<.05 Platinum-Y <.05<.05<.05 Double-counted data at 2 yr, 3 yr (Goto is preliminary report of Takada)

* James, Spiro, O'Donnell, et al. (2003) study included by Fried, Morris, Poole, et al. (2004) only in informal post-hoc analysis; M-H: Mantel-Haenszel stratified-adjusted analysis; M-R: meta-regression; N: no; NS: not significant; OR: odds ratio; OS: overall survival; P-OR: Peto odds ratio; Q: heterogeneity statistic; RD: risk difference; RR: risk ratio; RTx: radiation therapy; X: included; Y: yes.

Summary. This meta-analysis indicates that the findings of Fried, Morris, Poole, et al. (2004) are not reproducible when different pooling methods are used and 3 additional studies are included. We found evidence of publication bias at both 2 and 3 years, while Fried, Morris, Poole, et al. (2004) found it at neither time. Significant heterogeneity was observed at 2 years here but not at 3 years. Thus, we used a random effects model at 2 years and a fixed effects model at 3 years, but Fried, Morris, Poole, et al. (2004) did not find significant heterogeneity at either period and used only fixed effects models. While Fried, Morris, Poole, et al. (2004) reported a significant advantage for early TRTx at 2 years and nonsignificance at 3 years, nonsignificant results were obtained here at both periods.

Subgroups including studies using hyperfractionation or platinum yielded significant advantages for early TRTx at 2 years in both Fried, Morris, Poole, et al. (2004) and this meta-analysis. At 3 years, Fried, Morris, Poole, et al. (2004) reported that both subgroups retained significance, while here only hyperfractionation was significant. The current meta-regression found hyperfractionation to be nearly significant (p=0.07) at 2 years; hyperfractionation was significant at 3 years (p=0.04) and platinum was nearly significant at 3 years (p=0.06). Fried, Morris, Poole, et al. found that hyperfractionation and platinum predicted heterogeneity in risk differences.

As an exercise, we ran multiple variable meta-regression models, but none were significant at either period. In particular, hyperfractionation and platinum were not significant independent predictors here in multiple variable models. In contrast, Fried, Morris, Poole, et al. (2004) found larger effects when the variables were combined. Any meta-gresssion with multiple variables models is limited by the risk of overfitting when the pool of studies is small.

Conclusions

All but one of the studies selected for Key Questions 1 and 2 can be viewed as comparing early and late TRTx. Therefore, these studies were pooled to give a more robust analysis of early versus late TRTx. Overall, we did not find significant reductions in 2- and 3-year mortality for early TRTx over late TRTx. The RR at 2 years was 0.921 (95 percent CI: 0.844–1.005) and the RR at 3 years was 0.991 (0.955, 1.029). Although the overall analysis was nonsignificant, sensitivity analysis suggests that if there is an advantage favoring early TRTx it would seem to depend on use of hyperfractionation and possibly use of platinum chemotherapy.

Key Question 3

For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering TRTx? Comparisons of interest include:

- accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens ($\leq$10 Gy per week) versus split courses delivered over the standard interval; and

- single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).

Overview

Two randomized controlled trials (RCTs) compared one versus two fractions per day for previously-untreated limited stage SCLC (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000 [hereafter referred to as "Turrisi/Yuen"]; Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999 [hereafter referred to as "Schild/Sloan/Bonner"]; N=678). No other randomized trials directly compared dose rates, treatment intervals or fractionation schemes. Summary Table 26 summarizes selected characteristics; further details are in Appendix Tables 3A-C, 3H.*

Summary Table 26 Selected study characteristics of RCTs comparing one versus two fractions per day

study	N		chemoTx regimen	TRTx dose, Gy		# fractions x size; TRTx duration		TRTx started	PCI?
	2/d	1/d		2/d	1/d	2/day	1/day		
Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000	211	206	PE	45	45	30 x 1.5 Gy; 3 wks	25 x 1.8 Gy; 5 wks	week 1	yes
Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999	130	131	PE	48	50.4	32 x 1.5 Gy; 6 wks*	28 x 1.8 Gy; 6 wks	week 13	yes

* Split course: 16 fractions over 1.5 weeks, 2.5 weeks rest, then final 16 fractions over 1.5 weeks
Abbreviations table provided at the end of the Report.

Interventions. While total radiation doses were similar (45–50 Gy), and each trial compared one versus two fractions per day, they differed with respect to TRTx timing relative to chemotherapy cycles and other regimen features. The Turrisi/Yuen trial began TRTx in week one of cycle one, used the same total dose (45 Gy) in each arm, and gave radiation continuously (5 days/week for 3 or 5 weeks) in each arm. Thus, patients randomized to two fractions per day received 3 Gy daily and 15 Gy weekly, while those randomized to one fraction per day received 1.8 Gy daily and 9 Gy weekly.

The Schild/Sloan/Bonner trial administered three chemotherapy cycles, then restaged and randomized patients and began TRTx at week 13. Patients whose tumor had progressed during the initial three cycles were excluded if a single radiation field no longer encompassed the full extent of disease. Those randomized to two fractions per day received two split courses, each 24 Gy over 1.5 weeks, separated by 2.5 weeks' rest. Those randomized to one fraction per day received 50.4 Gy over 6 weeks, as 5 days/week of continuous TRTx. Thus, patients in the two-per-day arm received 3 Gy each treatment day, and 16 Gy/week in each of two 1.5 week courses. Those in the one-per-day arm received 1.8 Gy daily and 9 Gy weekly for 5 weeks and 3 days.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Both RCTs used cisplatin-etoposide chemotherapy (Summary Table 26). However, cisplatin dose in the Turrisi/Yuen trial was 60 mg/m^2 each 21-day cycle, but was 30 mg/m^2 each 28 day cycle in the Schild/Sloan/ Bonner trial (Appendix Table 3C).*

Study Populations. Each trial's study population had relatively good prognosis, and was well-balanced across arms for consistently reported baseline characteristics (Summary Table 27, Appendix Table 3B).* More than 90 percent of patients had good performance status (PS) of 0-1 at enrollment. Median or mean age ranged from 61 to 63 years across arms. Each trial enrolled mostly men (41 percent to 43 percent women across arms). Each reported the proportion of patients with weight loss at entry, and few (1–5 percent) had lost more than 10 percent.

The two trials did not consistently report other prognostic factors or baseline characteristics (Appendix Table 3B).* One trial reported both the proportion with disease outside the lung and the patients' racial distribution (Turrisi/Yuen). The other trial stratified patients by response to initial chemotherapy (Schild/ Sloan/Bonner). Neither trial reported the proportion of former or current smokers.

Study Quality and Reporting. Both trials were multicenter studies, published in full, and rated as good quality.

Results

The Turrisi/Yuen trial, using immediate concurrent TRTx, found that overall survival (OS) significantly favored the 2/day arm (Summary Table 28). The trial (n=211 2/day arm, 206 1/day arm) reported significantly longer median OS (23 versus 19 months; HR=1.2, 95 percent CI: 1.0–1.6; p=0.04) and greater 2- and 5-year survival (47 percent versus 41 percent, and 26 percent versus 16 percent, respectively) with two fractions per day (Turrisi/Yuen). However, the difference in failure-free survival at 2 years (29 percent versus 24 percent) was not statistically significant (p=0.10). Between-arm differences in response rates also were not statistically significant (Appendix Table 3F).*

Using late TRTx and split course therapy in the 2/day arm, Schild/Sloan/Bonner reported no significant difference between arms in overall (p=0.68) or progression-free (p=0.68) survival. Since this trial stratified patients by responses to three cycles of chemotherapy given before randomization, excluded any whose disease progressed substantially, and used an extended split-course rather than accelerated schedule in the 2/day arm, response rates could not be compared across arms or trials in a meaningful way.

Neither trial reported quality of life outcomes (Appendix Table 3F).*

The trials differed with respect to the frequency and/or between-arm comparisons of some adverse events, but were similar for others (Summary Table 29). Schild/Sloan/Bonner reported 3 percent treatment-related deaths in the 2/day arm and none in the 1/day arm (p=0.04), while Turrisi/Yuen reported similar rates in each arm (2–3 percent). Turrisi/Yuen reported no significant differences between arms in the proportion of patients experiencing one or more grade 3 (25 percent versus 23 percent), or grade 4 (62 percent versus 63 percent) toxicities. In contrast, Schild/Sloan/ Bonner reported significantly more patients in the 2/day arm than the

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

1/day arm with a non-hematologic toxicity of grade $\geq$3 (54.6 percent versus 38.9 percent, p=0.01) or grade 5 (3 percent versus zero, p=0.04).

Summary Table 27. Sample and Methods: Alternative Fractionations Schemes (once versus twice daily)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000 multicenter trial 5/89-7/92	Total 417 1 F/d 206 2 F/d 211	md (rng) 63 (34-80) 61 (30-82)	 41 42	0 1 2 3 43 51 5 39 55 5	PE (4 x 21 day cycles; 1 or 2 during, 2 or 3 after TRTx)	Dose 1 F/d: 45 Gy 2 F/d 45 Gy	Schedule 1.8 Gy/frac, 5 d/wk, 5 wks, begun in 1st wk of CTx 1.5 Gy/frac, 5 d/wk, 3 wks, begun in 1st wk of CTx	PCI? 10 x 2.5 Gy, if CR same
Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999 multicenter trial 9/90 -11/96	Total 261 1 F/d 131 2 F/d 130	mn (rng) 61.8 (38-81) 62.1 (37-79)	 42.0 43.1	0-1 2 97.7 5.3 93.1 6.9	PE (6 x 28 day cycles; 3 before, 2 during, 1 after TRTx)	Dose 1 F/d: 50.4 Gy 2 F/d 48 Gy	Schedule 28 x 1.8 Gy fracs, 38 d, 1st 39.6 Gy in AP-PA fields, last 10.8 Gy in oblique fields excluding spine, wks 13-16 32 x 1.5 Gy fracs; ≥4 hours apart; split course (16 fracs in 1.5 weeks; 2.5 weeks rest; then 16 fracs in 1.5 weeks)	PCI? 15 x 2 Gy if CR same

Abbreviations table provided at the end of the Report.

Summary Table28. Survival Outcomes: Alternative Fractionations Schemes (once versus twice daily)

Study	N		Overall Survival Med	1 yr	2 yr	3 yr	4 yr	5 yr	Failure- or Progression-Free Survival Med	1 yr	2 yr	3 yr	4 yr	5 yr
Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000	1 F/d	206	19	~75%	41%	~32%	~29%	16%	FFS:		24%			
	2 F/d	211	23	~70%	47%	~28%	~20%	26%			29%			
	Difference		4 (log-rank p=0.04; HR 1.2, 95% CI: 1.0, 1.6)	~5%	6%	~4%	~9%	10%			5% (p=0.10)			
Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999 multicenter trial 9/90 -11/96	1 F/d	131	20.6	~74%	44%	~33%	~23%	20.4%	PFS: ~14	~57%	31.3%	~25%	~23%	19.8%
	2 F/d	130	20.6	~74%	44%	~31%	~26%	22%	~14	~58%	30.8%	~27%	~21%	21%
	Difference		0 (p=0.68, log-rank)	0%	0%	-2%	3%	1.6%	0 (p=0.68, log-rank)	1%	-0.5%	2%	-2%	1.2%

Abbreviations table provided at the end of the Report.

Summary Table 29. Adverse Events: Alternative Fractionations Schemes (once versus twice daily)

Toxicity Type	Study	Severity or Grade	1 F/d n	%	2 F/d n	%	p	Not Reporting
Treatment-related mortality	Turrisi 1999 Yuen 2000		203	2	206	3	NS	
	Bonner 1999 Sloan 2002 Schild 2004		131	0	130	4	0.04	
Nausea/Vomiting	Turrisi 1999 Yuen 2000	grade 3 vomiting grade 4 vomiting	203	8 2	206	8 1	 NS (3+4)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3 nausea ≥ grade 3 vomiting	132	16.7 12.1	130	16.9 14.6	NS NS	
Anorexia	Turrisi 1999 Yuen 2000	grade 3 weight loss grade 4 weight loss	203	3 0	206	2 0	 NS (3+4)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	3.0	130	2.3	NS	
Lethargy	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	3.0	130	7.7	NS	Turrisi 1999/Yuen 2000
Neurosensory	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	7.6	130	11.5	NS	Turrisi 1999/Yuen 2000
Hearing loss	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	1.5	130	3.8	NS	Turrisi 1999/Yuen 2000
Esophagitis	Turrisi 1999 Yuen 2000	grade 3 grade 4	203	11 5	206	27 5	<0.001	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	5.3	130	12.3	0.05 (per investigators; 0.074 by corrected χ^2)	
Bronchopulmonary	Turrisi 1999 Yuen 2000	grade 3 grade 4 & 5	203	3 1	206	4 2	 NS (3-5)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	4.5	130	6.2	NS	
Pneumonitis	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	4.5	130	6.2	NS	Turrisi 1999/Yuen 2000
Kidney								Turrisi 1999/Yuen 2000; Bonner 1999/Sloan 2002/Schild 2004
Anemia	Turrisi 1999 Yuen 2000	grade 3 grade 4	203	23 3	206	23 5	 NS (3+4)	
	Bonner 1999 Sloan 2002 Schild 2004	≥ grade 3	132	3.0	130	2.3	NS	

Summary Table29. Adverse Events: Alternative Fractionations Schemes (once versus twice daily) (cont'd)

Toxicity Type	Study	Severity or Grade	1 F/d	n	%	2 F/d	n	%	p	Not Reporting
Thrombocytopenia	Turrisi 1999	grade 3	203	16		206	13			
	Yuen 2000	grade 4		8			8		NS (3+4)	
	Bonner 1999	≥ grade 3	128	60.9		127	45.7		0.0145	
	Sloan 2002	grade 4		24.2			20.5		NS	
	Schild 2004									
Leukopenia or neutropenia	Turrisi 1999	grade 3	203	41		206	38		NS (3+4)	
	Yuen 2000	grade 4		39			44		NS	
	Bonner 1999	≥ grade 3	128	88.3		127	89.8		NS	
	Sloan 2002	grade 4		37.5			36.2		NS	
	Schild 2004									
Hemoglobin	Bonner 1999	≥ grade 3	128	5.3		127	3.8		NS	Turrisi 1999/Yuen 2000
	Sloan 2002									
	Schild 2004									
Infection	Turrisi 1999	grade 3	203	6		206	6			
	Yuen 2000	grades 4 & 5		2			3		NS (3-5)	
	Bonner 1999	≥ grade 3	132	2.3		130	3.8		NS	
	Sloan 2002									
	Schild 2004									
Other	Turrisi 1999	one or more grade 3, no grade 4	203	23		206	25		NS	
	Yuen 2000	one or more grade 4, no grade 5		63			62		NS	
	Bonner 1999	any hematologic, ≥ grade 3	131	90.1		130	89.2		NS	
	Sloan 2002	any hematologic,, ≥ grade 4		43.5			42.3		NS	
	Schild 2004	any nonhematologic, ≥ grade 3		38.9			54.6		0.01	
		any nonhematologic, ≥ grade 4		9.2			13.8		NS	
		any nonhematologic, grade 5		0.0			3.1		0.04	
		any toxicity, ≥ grade 3		91.6			92.3		NS	
		any toxicity, ≥ grade 4		46.6			46.9		NS	
		any toxicity, grade 5		0.0			3.1		0.04	

With respect to hematologic toxicities, Schild/ Sloan/Bonner reported substantially more grade ≥3 thrombocytopenia (46 percent and 61 percent for 2/day and 1/day, respectively) than did Turrisi/Yuen (21 percent and 24 percent for 2/day and 1/day, respectively). The difference significantly favored the 2/day arm in Schild/Sloan/Bonner. However, grade 4 thrombocytopenia did not differ significantly between arms in either trial. Neither trial reported a significant difference between arms in incidence of grade ≥3 anemia, but it was substantially more common with early TRTx and larger cisplatin doses (Turrisi/Yuen; 26 percent and 28 percent) than with late TRTx and smaller cisplatin doses (Schild/Sloan/Bonner; 3 percent and 2.3 percent). Grade ≥3 leukopenia/ neutropenia was common in both trials, and did not differ across arms in either (≥80 percent in each).

With respect to non-hematologic toxicities, esophagitis was more common with twice daily than with once daily TRTx in each trial. Esophagitis also appeared more common in the Turrisi/Yuen trial, which used an accelerated schedule in the hyperfractionated arm, than in the other study, which used a split-course schedule. Both trials reported no significant differences between arms in incidence of vomiting, anorexia, bronchopulmonary effects, and infections. Grade ≥3 vomiting was not uncommon (9–15 percent). The other grade ≥3 adverse events reported by both trials each occurred in ≤10 percent of patients. Only Schild/Sloan/Bonner reported on lethargy, neurosensory effects, hearing loss, and pneumonitis. Between-arm differences were not statistically significant for any of these adverse events.

Conclusions

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited. One RCT suggests that starting TRTx with the first cycle of cisplatin-etoposide chemotherapy and giving it in two daily fractions over 3 weeks increases overall survival when compared with the same dose begun at the same time but given in one daily fraction over 5 weeks. Evidence from a second trial is difficult to interpret, since multiple variables were studied simultaneously. However, it found no difference in overall survival between treatment arms managed with one versus two fractions per day. Neither trial reported data on quality of life. Esophagitis was the only adverse event reported more frequently with two fractions per day than with one fraction per day in both trials.

Key Question 4

What are the relative benefits and harms (survival, toxicity, and quality of life) of adding TRTx to chemotherapy for primary treatment of extensive-stage SCLC?

Overview

Five small RCTs compared outcomes of chemotherapy with versus without TRTx for previously-untreated extensive stage SCLC (N=238; 110–135 randomized to +TRTx, 103–128 to -TRTx). Summary Table 30 summarizes selected characteristics of these trials; more complete

details are in Summary Table 31 and Appendix Tables 4A-C, 4H.* The Jeremic, Shibamoto, Nikolic, et al. (1999) trial randomized 109 patients; other trials were smaller, ranging from 18 to 54 patients.

Interventions. Of the five available trials, only Jeremic, Shibamoto, Nikolic, et al. (1999) tested effects of TRTx in the context of current treatment strategies (regimens, doses, and schedules). Although both Jeremic, Shibamoto, Nikolic, et al. (1999) and Lebeau, Chastang, Brechot, et al. (1993) used platinum-etoposide chemotherapy regimens, only Jeremic, Shibamoto, Nikolic, et al. (1999) administered chemotherapy and radiation concurrently. Lebeau, Chastang, Brechot, et al. (1993) gave radiation therapy after all chemotherapy was completed (sequential administration), while the other three trials alternated chemotherapy and radiation and did not use platinum-based chemotherapy. Also noteworthy are the wide range of radiation doses used by Lebeau, Chastang, Brechot, et al. (1993), and the low dose and unusual schedule of TRTx used by Brincker, Hindberg, Hansen, et al. (1987).

Another study design feature, unique to Jeremic, Shibamoto, Nikolic, et al. (1999) (Appendix Table 4A),* permits outcomes of randomized (chemotherapy-responsive) patients to be compared with those of nonrandomized patients who responded less completely outside the chest. All patients registered for this trial received 3 cycles of cisplatin/etoposide (PE) before randomization. To be eligible for the RCT, patients had to achieve a complete response (CR) outside the thorax and respond at least partially (PR) in the thorax after three PE cycles. Those who achieved only a PR outside the thorax, and those with less than PR in either site, were not randomized, but were treated with chemotherapy plus TRTx and followed.

Study Populations. Only Jeremic, Shibamoto, Nikolic, et al. (1999) limited enrollment to extensive-stage disease (ESD) patients. The others included both stages (Appendix Table 4A),* but reported at least one outcome separately by arm for those with ESD. Rosenthal, Tattersall, Fox, et al. (1991) did not report the number of ESD patients per treatment arm.
Data on baseline characteristics showed that ESD patients enrolled in each arm of Jeremic, Shibamoto, Nikolic, et al. (1999) and Nou, Brodin, and Bergh (1998) were similar (Summary Table 31, Appendix Table 4B).* The other RCTs pooled baseline characteristics for extensive- and limited-stage patients (Lebeau, Chastang, Brechot, et al., 1993; Brincker, Hindberg, Hansen, et al., 1987) or for all participants (Rosenthal, Tattersall, Fox, et al., 1991), thus similarity of ESD patients was uncertain.

Most patients in Jeremic, Shibamoto, Nikolic, et al. (1999) had good performance at enrollment (67 percent with Karnofsky scores 90-100, excluded if $\leq$60), while Nou, Brodin, and Bergh (1998) included many with poorer performance (median Karnofsky score 60, range 30–90). Median age ranged from 59 to 65 years across study arms. Both trials enrolled mostly men (25 percent to 41 percent women across arms). Just over half of patients in each trial had $\geq$2 metastatic sites (50 percent to 58 percent across arms; Appendix Table 4B).† Less than half of patients in Jeremic, Shibamoto, Nikolic, et al. (1999) had lost $\geq$5 percent of body weight at enrollment, but Nou, Brodin, and Bergh (1998) did not report this potential marker of poor prognosis. Neither trial reported distributions by race.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.
† Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Study Quality and Reporting. All five trials were published in full, but only two were multicenter studies (Lebeau, Chastang, Brechot, et al., 1993; Rosenthal, Tattersall, Fox, et al., 1991) and only Nou, Brodin, and Bergh (1998) was a good-quality trial. Jeremic, Shibamoto, Nikolic, et al. (1999) was of fair quality since it did not report on methods used for randomizing patients. The other three were of poor quality to evaluate the role of TRTx for ESD patients (Appendix Table 4H).* Data were unavailable for each of the poor quality trials to evaluate the comparability of randomized ESD patients; two had excessive loss to follow-up (Rosenthal, Tattersall, Fox, et al. 1991; Brincker, Hindberg, Hansen, et al., 1987), and each failed to analyze and report all important outcomes separately for ESD patients.

Summary Table 30. Selected Characteristics of RCTs Comparing Chemotherapy with versus without TRTx

study	N		Pt?	chemoTx regimen	TRTx timing*	TRTx dose	TRTx schedule; fractionation	PCI?	# centers	quality rating
	+TRTx	-TRTx								
Jeremic, Shibamoto, Nikolic, et al., 1999	55	54	yes	PE/CbE	concurrent	54 Gy	wks 10-13; 36 x 1.5Gy, 2/d	yes	one	fair
Nou, Brodin, and Bergh, 1988	28	26	no	CAVML	alternating	40 Gy	wks 10-13; 20 x 2 Gy, 1/d	no	one	good
Lebeau, Chastang, Brechot, et al., 1993	10	8	yes	LCAE/PEVe	sequential	32-65 Gy	wks 36-39; 2 Gy fracs, 1/d	some	multi	poor
Rosenthal, Tattersall, Fox, et al., 1991	27 total; N/arm NR		no	M-CAV	alternating	40 Gy	wks 10-?; 20 x 2 Gy, ?/d	?	multi	poor
Brincker, Hindberg, Hansen, et al., 1987	16	14	no	CAV/LME	alternating	12 Gy	days 60 and 100; 6 Gy each	?	one	poor

* Timing relative to chemotherapy administration
Abbreviations table provided at the end of the Report.

Summary Table 31. Sample and Methods: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
Jeremic, Shibamoto, Nikolic, et al., 1999[1] single center: 01/88 – 06/93	Total 109 +TRTx 55 -TRTx 54 nonrandomized CR/PR: 34 PR/PR: 28 SD/PD 35	md (rng) 59 (38-70 59 (39-71)	 40 41	100 90 80 70 31 36 18 15 24 43 18 15 KPS	PE/Cb-E	Dose 54 Gy	Schedule 24 x 1.5 Gy fracs; 2 frac/d, over 2.5 wks, then 12 x 1.5 Gy fracs, 2 frac/d over 6 d	PCI? 25 Gy, 10 fracs
Nou, Brodin, and Bergh, 1988[2] single center 01/80 - 12/83 (ESD only)	Total 54 +TRTx 28 -TRTx 26	md (rng) 65 (55-78) 60 (41-81)	 25 31	med (rng) 60 (30-90) 60 (30-90) KPS	cytoxan, vincristine, doxorubicin, methotrexate, lomustine	Dose 40 Gy	Schedule 1 frac/d, 2 Gy each, 5 d/wk, over 4 wks	PCI? No
Lebeau, Chastang, Brechot, et al., 1993[3] 27 centers 10/85 - 04/88	Total 18 +TRTx 10 -TRTx 8	≥ 60 48 38.5	 4 8	90-100 70-80 60 63 22 15 46 50 4 KPS	CCNU, cytoxan, doxorubicin, etoposide, cisplatin, vindesine	Dose mn 46.5 Gy (rng: 32-65 Gy)	Schedule begun 4 wks after last CTx cyc; varied schedules: 32 Gy in 9 frac over 11-18 d to 65 Gy in 33 frac over 64 d vincristine,	PCI? some, but N/arm uncertain for ESD
Rosenthal, Tattersall, Fox, et al., 1991[3] 3 centers 01/77 - 07/79	Total 27 +TRTx ? -TRTx ?	md (rng) 60 (26-77)	 24	0 1 2 ? 1 88 3 8	cytoxan, vincristine, doxorubicin; + methotrexate (IV or intra-thecal)	Dose 40 Gy	Schedule 20 fracs between CTx cycs 3, 4	PCI? not specified

Abbreviations table provided at the end of the Report.

Summary Table 31. Sample and Methods: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD) (continued)

Study	N	Age	% Female	% Performance Status	CTx Regimen	RTx Regimen		
				0 1 2 3		Dose	Schedule	PCI?
Brincker, Hindberg, Hansen, et al., 1987[3]	Total 30	md (rng)			cytoxan, vincristine,			
	+TRTx 16	60 (42-69)	27	34 51 15	doxorubicin, methotrexate	12 Gy	2 fracs, 6 Gy each, day 60 to upper hemi-body and day 100 to lower hemi-body	not specified
single center	-TRTx 14	63 (46-69)	27	24 57 19	, lomustine, etoposide			
03/81 - 01/84								

[1] enrollment limited to ESD patients; [2] enrolled ESD & LSD patients, and reported characteristics of each separately;
[3] enrolled ESD & LSD patients, but only reported characteristics for the two groups pooled

Results

Jeremic, Shibamoto, Nikolic, et al. (1999) reported that adding concurrent TRTx to platinum-based chemotherapy for good-performance patients selected by their response to an initial 3 cycles of platinum-etoposide (PE) significantly improved overall survival (median OS, 17 versus 11 months; 2- and 3-year OS, 38 percent versus 28 percent and 22 percent versus 13 percent respectively; p=0.041) and relapse-free survival (median RFS, 13 versus 9 months; 2- and 3-year RFS, 35 percent versus 22 percent and 20 percent versus 9 percent, respectively; p=0.045) (Summary Table 32). Jeremic, Shibamoto, Nikolic, et al. (1999) also reported that adding TRTx to chemotherapy for these selected patients significantly increased CR rates in the thorax at week 21 (96 percent versus 66 percent; p=0.00005) (Appendix Table 4F). However, the improvement in duration of CRs in the thorax did not achieve statistical significance (mean, 22$\pm$26 versus 14$\pm$16 months; p=0.055).

Only 3% of non-randomized patients who achieved PR outside the thorax and CR in the thorax after three cycles of PE survived at 3 years, despite TRTx and additional chemotherapy (Summary Table 32). Furthermore, no patients who achieved only PR at each site survived at three years. However, data are unavailable to compare these outcomes with similar patients managed without TRTx.

No other trial reported a statistically significant effect of TRTx on survival of ESD patients (Summary Table 32). This includes Lebeau, Chastang, Brechot, et al. (1993), which only randomized patients in CR after eight cycles of chemotherapy (Appendix Tables 4A, 4F)[*] and used a chemotherapy regimen with cisplatin (Summary Table 31). Whether the absence of a significant effect reflects the small size and inadequate statistical power of these trials, or is attributable to their use of chemotherapy regimens, timing and sequencing of TRTx, or radiation doses and schedules that differed from those used in Jeremic, Shibamoto, Nikolic, et al. (1999) is uncertain, since available data are insufficient.

None of the trials reported data on quality of life (Appendix Table 4F).[*] Jeremic, Shibamoto, Nikolic, et al. (1999) reported significantly more grade 3 and 4 esophagitis (27 percent versus zero, p=0.0002), but significantly less grade 3 and 4 nausea and vomiting (9 percent versus 34 percent, p=0.0038) and renal toxicity (zero versus 22 percent, p=0.001) in the arm given TRTx (Summary Table 33). No other statistically significant differences between arms were reported for adverse events.

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Summary Table 32. Survival Outcomes: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD)

Study	N	OS Med	1 yr	2 yr	3 yr	4 yr	5 yr	RFS Med	1 yr	2 yr	3 yr	4 yr	5 yr
Jeremic,1999[1]	+TRTx 55	17	65%	38%	22%	13%	9.1%	13	56%	35%	20%	13%	9.1%
	-TRTx 54	11	46%	28%	13%	5.6%	3.7%	9	41%	22%	9.3%	5.6%	1.9%
	Difference	6	19%	10%	9%	7.4%	5.4%	4	15%	13%	10.7%	7.4%	7.2%
		(p=0.041 by log-rank test)											
		unrandomized groups by post-3rd cycle response (thorax/ elsewhere):											
	CR/PR: 34	8	35%	8.8%	2.9%	0%	0%	6	26%	5.9%	0%	0%	0%
	PR/PR: 28	6	21%	3.6%	0%	0%	0%	5	18%	0%	0%	0%	0%
	SD/PD 35	3	0%	0%	0%	0%	0%	NR	0%	0%	0%	0%	0%
Nou 1988[2]	+TRTx 28	9.2	32%	0%	0%	0%							
	-TRTx 26	7.6	26%	0%	0%	0%							
	Difference	1.6	6%	0%	0%	0%							
		(chi-square 0.045, 0.8<p<0.9, by life-table analysis)											
Lebeau 1993[3]	+TRTx 10	~6.3	~10%	~10%	0%	0%	0%						
	-TRTx 8	~7.0	~25%	~12%	~12%	0%	0%						
	Difference	-0.7	-15%	-2%	-12%	0%	0%						
		(p = 0.43 by log-rank test)											
Rosenthal 1991[3]	Total 27												
	+TRTx ?	5 (95% CI: 2-8)											
	-TRTx ?	7 (95% CI: 3-10)											
	Difference	-2											
		(p=0.796)											
Brincker 1987[3]	+TRTx 16	7	~25%	0%	0%	0%	0%	7	~23	0%	0%	0%	0%
	-TRTx 14	10	~30%	0%	0%	0%	0%	8.5	~26	0%	0%	0%	0%
	Difference	-3	-5%	0%	0%	0%	0%	-1.5	-3%	0%	0%	0%	0%
		(p = 0.44)						(p = 0.45)					

[1] enrollment limited to ESD patients; [2] enrolled ESD & LSD patients, and reported characteristics of each separately;
[3] enrolled ESD & LSD patients, but only reported characteristics for the two groups pooled

Summary Table 33. Adverse Events: Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD)

Toxicity Type	Study	Severity or Grade	+TRTx n	+TRTx %	-TRTx n	-TRTx %	p	Not Reporting
Treatment-related mortality	Nou 1988		28	4	26	4	NS	Jeremic 1999; Lebeau 1993; Rosenthal 1991; Brincker 1987
Nausea/Vomiting	Jeremic 1999	acute grades 3/4 nausea and vomiting	55	9	54	34	0.0038	Nou 1988; Lebeau 1993; Rosenthal 1991
	Brincker 1987		"no significant differences between the two treatment groups"					
Anorexia								Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Lethargy								Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Neurosensory	Brincker 1987		"no significant differences between the two treatment groups"					Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991
Hearing loss								Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Esophagitis	Jeremic 1999	acute grades 3/4 esophageal	55	27	54	0	0.0002	Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Bronchopulmonary	Jeremic 1999	acute grade 3 (no grade 4, either arm)	55	5	54	0	0.082	Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Pneumonitis	Brincker 1987		no cases observed					Jeremic 1999; Nou 1988; Lebeau 1993; Rosenthal 1991
Kidney	Jeremic 1999	acute grades 3 or 4	55	0	54	22	0.001	Nou 1988; Lebeau 1993; Rosenthal 1991; Brincker 1987
Anemia	Jeremic 1999	acute grades 3 or 4	55	11	54	20	0.39	Lebeau 1993; Rosenthal 1991
	Nou 1988	hemoglobin nadir	Similar medians and ranges between groups					
	Brincker 1987	hemoglobin <6 mmol/L	41 (LSD+ESD)	~50	37 (LSD+ESD)	~27		
Thrombocytopenia	Jeremic 1999	acute grades 3/4	55	27	54	42	0.23	Lebeau 1993; Rosenthal 1991
	Nou 1988	thrombocyte count nadir (10^9/L)	Similar medians between groups					
	Brincker 1987	platelets <75x10^3/μl	41 (LSD+ESD)	~65	37 (LSD+ESD)	~10		

Summary Table 33. Adverse Events, Chemotherapy with versus without Thoracic Radiation Therapy, Extensive Stage Disease (ESD), (continued)

Toxicity Type	Study	Severity or Grade	+TRTx n	+TRTx %	-TRTx n	-TRTx %	p	Not Reporting
Leukopenia or neutropenia	Jeremic 1999	acute grade 3/4 leukopenia	55	44	54	61	0.18	Lebeau 1993; Rosenthal 1991
	Nou 1988	leukocyte count nadir (10^9/L)	Similar medians and ranges between groups					
	Brincker 1987	leukocytes < $2.5x10^3/\mu l$	41 (LSD+ESD)	~37	37 (LSD+ESD)	~18		
Infection	Jeremic 1999	acute grades 3-5	55	23	54	33	0.64	Lebeau 1993; Rosenthal 1991
	Nou 1988	septicemia	Similar medians and ranges between groups					
	Brincker 1987	febrile episodes	No significant differences between arms					
Other	Jeremic 1999	combined late grades 3/4 toxicities	55	5	54	0	0.082	Lebeau 1993; Rosenthal 1991
	Nou 1988	"other serious side effects"	28	29	26	8	NS	
	Brincker 1987	tolerated 75-100% of CTx doses in cycles after hemibody RTx completed	28 (LSD+ESD)	25	32 (LSD+ESD)	91		

Conclusions

Evidence from one small single-center randomized trial suggests adding concurrent TRTx to chemotherapy may improve survival of ESD patients who respond to an initial three cycles of PE chemotherapy with a CR outside the thorax and at least a PR in the thorax. Uncontrolled data from the same trial suggest that there is little to no benefit from adding TRTx to chemotherapy for ESD patients who achieve no better than a PR outside the thorax after three cycles of PE. With the regimens used in Jeremic, Shibamoto, Nikolic, et al. (1999), concurrent TRTx apparently increases grades 3 and 4 esophagitis.

No other trials were able to reproduce the results reported by Jeremic, Shibamoto, Nikolic, et al. (1999). Limitations of these trials include small sample sizes lack of a platinum-containing drug in their chemotherapy regimens, and use of nonconcurrent TRTx.

Key Question 5

What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation (PCI) for patients with SCLC in complete remission (CR) after primary therapy?

Overview

The literature search identified seven RCTs comparing primary therapy for SCLC with versus without PCI (Summary Table 34). One of these was excluded because randomization and PCI preceded completion of primary therapy and evaluation of response (n=51; Niiranen, Holsti, and Salmo, 1989). Thus, each arm included some patients with less than CR. A second was excluded because it also randomized patients to PCI or no PCI before response was known, and because an initial randomization assigned half the patients to radiotherapy without chemotherapy (n=104 in 4 groups; Seydel, Creech, Pagano, et al., 1985). The remaining five trials onlyrandomized patients who achieved CR after primary chemotherapy with or without TRTx (pooled N=922; Arriagada, Le Chevalier, Borie, et al., 1995/Arriagada, Le Chevalier, Riviere, et al., 2002; Laplanche, Monnet, Santos-Miranda, et al., 1998; Gregor, Cull, Stephens, et al., 1997; Ohonoshi, Ueoka, Kawahara, et al., 1993; Cao, Huang, and Tu, 2000).

Four of these five studies were included in a Cochrane review and meta-analysis that collected updated individual patient data from each RCT (Prophylactic Cranial Irradiation Overview Collaborative Group 2000; Auperin, Arriagada, Pignon, et al., 1999). Cao, Huang, and Tu (2000; n=51) was the exception. The Cochrane review also included one study published before 1985 (Aroney, Aisner, Wesley, et al., 1983; n=29) and two unpublished trials (Wagner, Kim, Turrisi, et al., 1996; Danish/NCI trial; pooled N=87) that were not identified by our literature search. Additionally, the Cochrane review collected data on randomized patients excluded from investigators' published analyses, permitting intent-to-treat analysis of results for 987 patients in CR from seven RCTs (526 randomized to PCI, 461 to no PCI). Finally, the Cochrane review collected individual patient data on duration of follow-up and on covariates at randomization including age, gender, extent of disease, performance status, induction regimen (chemotherapy with versus without TRTx), and time since initial therapy, to permit analyses that tested whether these covariates influenced the magnitude of benefit from PCI. The Cochrane

review excluded Niiranen, Holsti, and Salmo (1989) and Seydel, Creech, Pagano, et al. (1985) (as does this review), plus eight other RCTs published before 1985, for similar reasons (some randomized patients not in CR; pooled N=929).

Since individual patient data submitted for the Cochrane review included longer follow up and permitted analyses not possible with abstracted data from a literature-based systematic review, and since only one eligible study was published subsequently (Cao, Huang, and Tu, 2000; N=51), the Results section below summarizes and highlights the principal findings of the Cochrane review, and also summarizes results of the Cao, Huang, and Tu (2000) study.

Summary Table 34. RCTs of PCI versus no PCI for SCLC in CR

Study	N Randomized		all in CR?	Pt?	chemoTx regimen	TRTx	PCI Regimen			publication type
	+ PCI	no PCI					dose	fractions	duration	
Arriagada, Le Chevalier, Borie, et al., 1995	149	151	yes	some	various; # type NR	91%-93% each arm; reg. NR	24 Gy	8 x 3 Gy	12 days (4 d/wk)	full
Laplanche, Monnet, Santos-Miranda, et al., 1998	100	111	yes	??	various; # type NR	not reported	24-30 Gy	≤3 Gy each	≤3 weeks	full
Gregor, Cull, Stephens, et al., 1997	194	120	yes	some	various; # NR	84% each arm; reg. NR	8-40 Gy	2 Gy each	1-3+ weeks	full
Ohonoshi, Ueoka, Kawahara, et al., 1993	23	23	yes	no	same for all	all LS; 20 x 2 Gy/d	40 Gy	20 x 2 Gy	4 weeks	full
Aroney, Aisner, Wesley, et al., 1983	15	14	yes	no	same for all	not reported	30 Gy	10 x 3 Gy	2 weeks	full
Wagner, Kim, Turrisi, et al., 1996	17	15	yes	NR	not reported	57%; reg. NR	24 Gy	8 x 3 Gy	not reported	abstract
Danish/NCI	28	27	yes	NR	not reported	42%; reg. NR	24 Gy	8 x 3 Gy	not reported	none
Cao, Huang, and Tu, 2000	26	25	yes	some	two; # NR	all; 40-64 Gy 1.8-2 Gy/d	25-30 Gy	1.8-2 Gy ea.	2-3 weeks	full
Seydel, Creech, Pagano, et al., 1985	52	51	??	no	one; half only	all; 45 Gy 1.8-2 Gy/d	30 Gy	10 x 3 Gy	2 weeks	full
Niiranen, Holsti, and Salmo, 1989	25	26	no	no	two; half each	all; 25 x 2.2 Gy/d	40 Gy	20 x 2 Gy	4 weeks	full

Results

Cochrane Review and Meta-Analysis.

Study Characteristics. At the time of analysis, median follow-up for the control and PCI groups was 5.3 and 5.9 years, respectively; 846 of 987 randomized patients had died (PCI Overview Collaborative Group 2000; Auperin, Arriagada, Pignon, et al., 1999). Of seven included trials, three enrolled 84 percent of patients (Arriagada, Le Chevalier, Borie, et al., 1995/Arriagada, Le Chevalier, Riviere, et al., 2002; Laplanche, Monnet, Santos-Miranda, et al., 1998; Gregor, Cull, Stephens, et al., 1997) while the other four contributed 29 to 55 each (Aroney, Aisner, Wesley, et al., 1983; Wagner, Kim, Turrisi, et al., 1996; Ohonoshi, Ueoka, Kawahara, et al., 1993; Danish/NCI trial). The control (N=461) and PCI (n=526) groups were well balanced for gender (76–77 percent male), age (median 59 years, ranges 26–80 and 21–79), performance status (66–67 percent PS 0, 30–32 percent PS 1) and other covariates. Reviewers judged each trial to be methodologically sound, including adequate randomization and allocation concealment.

For most patients in these trials, the specific chemotherapy regimens used to induce CR were not reported but it is likely platinum-based regimens were used only for a minority. The large trials did not mandate a uniform chemotherapy regimen (Arriagada, Le Chevalier, Borie, et al., 1995/Arriagada, Le Chevalier, Riviere, et al., 2002; Laplanche, Monnet, Santos-Miranda, et al., 1998; Gregor, Cull, Stephens, et al., 1997). Only Gregor, Cull, Stephens, et al. (1997) reported the variety of regimens used, but since they did not report the proportion given each regimen, an unknown number of patients received cisplatin or carboplatin. Of the four smaller trials, Aroney, Aisner, Wesley, et al. (1983) and Ohonoshi, Ueoka, Kawahara, et al. (1993) each used a uniform regimen, but neither included a platinum drug. While Cochrane reviewers collected individual patient data on whether they received TRTx, information was unavailable (either in the review or in the original publications) on doses, fractionation schemes, or timing relative to chemotherapy. Summary Table 35 summarizes the review's pooled estimates of efficacy outcomes.

Summary Table 35. Meta-analytic Results for Efficacy Outcomes Reported in the Cochrane Review

Outcome	N evaluated		Hazard Ratio	95% CI		p	event-free at 3 yrs (by K-M)		
	+PCI	-PCI		lower	upper		+PCI	-PCI	difference
mortality	526	461	0.84	0.73	0.97	0.01	20.7%	15.3%	5.4%
disease-free survival	526	461	0.75	0.65	0.86	<0.00003			
brain metastasis	524	457	0.46	0.38	0.57	<0.00001	33.3%	58.6%	25.3%
non-brain metastasis	325	332	0.89	0.69	1.15	0.4			
loco-regional recurrence	323	334	0.97	0.75	1.26	0.8			

Mortality and Survival. Although six of seven included trials observed proportionally more deaths in the control arms, the hazard ratio (HR) for mortality did not significantly favor the PCI arm in any single trial. However, meta-analysis showed that PCI significantly decreased the likelihood of death (HR=0.84; 95 percent CI: 0.73–0.97; p = 0.01). Cox modeling to adjust for extent of disease, gender and age did not appreciably change the relative likelihood (HR=0.83;

p=0.009). The HR remained constant despite further adjustment for performance status, induction regimen (with versus without TRTx), and time from induction to randomization. Kaplan-Meier actuarial analysis estimated an absolute increase of 5.4 percent in the proportion of patients alive at 3 years (from 15.3 percent without PCI to 20.7 percent with PCI). The survival benefit persisted beyond 3 years, and there was no evidence of statistical heterogeneity among the seven included trials.

Other Efficacy Endpoints. The HR for brain metastasis significantly favored the PCI arm in five of seven trials; the Danish/NCI and Laplanche, Monnet, Santos-Miranda, et al. (1998) trials were the exceptions. Meta-analysis showed reduced likelihood of brain metastasis among those randomized to PCI (HR = 0.46; 95 percent CI: 0.38–0.57; p <0.001). Kaplan-Meier analysis estimated an absolute decrease of 25.3% in the cumulative rate of brain metastasis at 3 years (from 58.6 percent without PCI to 33.3 percent with PCI).

Additional analyses demonstrated that PCI increased the likelihood of disease-free survival (HR=0.75; 95 percent CI: 0.65–0.86; p < 0.001), but did not reduce extra-cerebral metastases (HR=0.89; 95% CI: 0.69–1.15; p=0.4) or locoregional recurrence (HR=0.97; 95% CI: 0.75–1.26; p=0.8). However, data on non-brain metastases and locoregional recurrence were available for only 67% of randomized patients.

PCI Dose-Response. Trials (and subgroups from different centers in Gregor, Cull, Stephens, et al., 1997) were divided by total radiation dose used for PCI: 8 Gy delivered in one fraction, 24–25 Gy delivered in 8–12 fractions, 30 Gy delivered in 10 fractions, and 36 or 40 Gy delivered in 18 or 20 fractions. Summary Table 36 summarizes results of this and other subgroup analyses.

Evidence was lacking for a trend towards smaller HR (greater impact on survival) with larger PCI dose (p = 0.89), but few patients were treated at the lowest and highest doses. In contrast, the HR to develop brain metastasis decreased significantly as PCI dose increased (p = 0.02), suggesting larger doses had a greater magnitude of beneficial effect.

Summary Table 36. Cochrane Review Subgroup Analyses for Mortality and Brain Metastasis

covariate	subgroups	mortality						brain metastasis					
		N evaluated		hazard ratio	95% CI		p	N evaluated		hazard ratio	95% CI		p
		+PCI	-PCI		lower	upper		+PCI	-PCI		lower	upper	
PCI dose	8 Gy	26	16	0.69	0.35	1.37	0.3	26	16	0.76	0.28	2.10	0.6
	24-25 Gy	330	340	0.88	0.75	1.04	0.12	329	338	0.52	0.41	0.67	<0.00001
	30 Gy	119	82	0.81	0.59	1.12	0.2	118	80	0.34	0.19	0.59	0.0002
	36-40 Gy	51	59	0.81	0.54	1.20	0.3	51	59	0.27	0.14	0.51	0.00001
age	≤54 yrs	147	158	0.84	0.65	1.08	0.18	147	157	0.55	0.39	0.77	0.0005
	55-64 yrs	250	185	0.90	0.73	1.11	0.3	248	184	0.49	0.35	0.68	<0.00002
	≥65 yrs	129	118	0.79	0.60	1.03	0.09	129	116	0.37	0.24	0.59	<0.0001
disease stage	limited	464	383	0.85	0.73	0.99	0.04	462	382	0.48	0.38	0.61	<0.00001
	extensive	62	78	0.77	0.54	1.11	0.16	62	75	0.38	0.23	0.64	0.0002
performance status	0	212	215	0.85	0.69	1.05	0.13	211	214	0.47	0.35	0.63	<0.00001
	1-3	103	111	0.78	0.58	1.04	0.09	103	110	0.50	0.32	0.78	0.003
induction therapy	+TRTx	314	248	0.86	0.71	1.03	0.10	314	248	0.43	0.33	0.57	<0.00001
	-TRTx	94	86	0.88	0.64	1.21	0.4	92	82	0.40	0.23	0.67	0.0005
gender	male	403	352	0.77	0.66	0.90	0.0009	401	348	0.47	0.37	0.60	<0.00001
	female	123	109	1.05	0.78	1.42	0.7	123	109	0.50	0.32	0.78	0.002
time from induction to randomization	<4 mos.	84	77	0.92	0.66	1.29	0.6	83	75	0.27	0.16	0.46	<0.00001
	4-6 mos.	127	152	0.79	0.61	1.02	0.07	126	150	0.50	0.35	0.72	0.0002
	>6 mos.	102	91	1.01	0.74	1.38	0.9	102	91	0.69	0.44	1.08	0.1

Subgroup Analyses. Patient subgroups were evaluated for differences in magnitude of benefit from PCI. Subgroups were defined by individual patient data on age (≤54 versus 55-64 versus ≥65 years), gender, disease stage at diagnosis (limited versus extensive), performance status (0 versus 1-3), induction regimen (with versus without TRTx), and time from beginning induction to randomization (<4 versus 4-6 versus >6 months). Only two subgroup comparisons suggested significant differences in benefit from PCI for overall survival or brain metastasis.

Results for males (n =755) showed statistically significant decreases in mortality (HR=0.77; 95 percent CI: 0.66–0.90; p = 0.0009) and brain metastasis (HR=0.47; 95 percent CI: 0.37–0.60; p<0.0001) among those randomized to PCI. However, results for females (n=232) showed no significant effect of PCI on survival (HR=1.05; 95 percent CI: 0.78–1.42; p=0.7) despite a significant effect on brain metastasis (HR=0.50; 95 percent CI: 0.32–0.78; p=0.0002). A statistical test for interaction of gender with treatment effect on survival was of borderline significance (p=0.07).

PCI delayed by <4 months from start of induction therapy (HR=0.27; 95 percent CI: 0.16–0.46; p<0.0001) or by 4 to 6 months (HR=0.50; 95 percent CI: 0.35–0.72; p=0.0002) significantly reduced the likelihood of brain metastasis. In contrast, PCI delayed >6 months (HR=0.69; 95 percent CI: 0.44–1.08; p=0.10) did not significantly decrease the likelihood of brain metastasis. Note that each fully published trial with some patients given PCI later than 6

months after induction (3 of 4 trials, with 95 percent of 193 patients in this subgroup) specified that patients were randomized to PCI or no PCI within 14 days of achieving CR. This trend (smaller effect on likelihood of brain metastasis as delay lengthened) was statistically significant (p=0.01). However, the relationship between time from induction therapy to PCI and hazard ratio for death did not show a similar statistically significant trend.

Adverse Events. The Cochrane review did not abstract and report data on adverse events. Of five fully-published studies, only Arriagada et al. (1995) reported acute events during PCI; these included fever or asthenia (24 percent), headache (24 percent), vomiting (10 percent), skin erythema (9 percent), and altered mood (6 percent). Adverse event data were unavailable from the two unpublished trials (Wagner, Kim, Turrisi, et al., 1996; Danish/NCI trial).

Two trials prospectively studied neuropsychological or cognitive sequelae of PCI in patients who survived ≥6 months from treatment (Arriagada, Le Chevalier, Borie, et al. 1995; Gregor, Cull, Stephens, et al., 1997; Table 37). The Gregor, Cull, Stephens, et al. (1997) trial also reported data on symptoms that affect quality of life (QoL). Each compared measurements at baseline with measurements at times after PCI. Information was unavailable on ages and other baseline characteristics of those tested for late neuropsychological or cognitive effects. Additionally, available evidence did not permit testing of the hypothesis that the likelihood of neuropsychological deficits may increase with increasing PCI dose.

In Arriagada, Le Chevalier, Borie, et al. (1995), neuropsychological assessments (made by a neurologist at baseline and late after PCI) included evaluation of higher brain function, mood, sensation, walking, cerebellar function, tendon reflexes, and sensibility. Additionally, blinded assessors reviewed pre- and post-PCI brain computed tomography (CT) scans for evidence of structural abnormalities (e.g., cortical atrophy or ventricular dilatation).

Summary Table 37. Adverse Effects Reported from RCTs of PCI versus no PCI

Study	acute toxicities reported ?	most common events	type of assessment	N random-ized	N eval-uated at base-line	# w no or only mild baseline deficits	#, time of reassessments	principal findings
Arriagada, Le Chevalier, Borie, et al., 1995	yes	fever 24% headache 24% vomiting 10%	neuropsy-chological; brain CT	total: 300 +PCI: 149 -PCI: 151	229 114 115	94 44 50	33 of 58 @ 18 mos. 23 of 35 @ 30 mos.	groups did not differ in # of new changes or abnormalities
Gregor, Cull, Stephens, et al., 1997	no		cognitive	total: 314 +PCI: 194 -PCI: 120	125 76 49	diff. tests: 44-58 29-37	59 of 106 @ 6 mos. 32 of 54 @ 1 yr 9 of 20 @ 2 yr	groups did not differ in # of new deficits
			symptoms affecting QoL	total: 314 +PCI: 194 -PCI: 120	not reported	diff tests: 11-21 7-14	re-assessed @ 6 mos., 1 & 2 yr; #'s not reported;	larger proportion of –PCI than of +PCI showed deterioration

Of 300 randomized patients, baseline assessments were available for only 229 (115 controls and 114 randomized to PCI). Only 50 control patients (43 percent) and 44 randomized to PCI (39 percent) were free of neuropsychological abnormalities at baseline assessment. Investigators re-assessed 33 of 58 patients alive at 18 months and 23 of 35 alive at 30 months. They reported no statistically significant differences between treatment groups with respect to appearance of further neuropsychological changes or CT scan abnormalities over two years from PCI. However, only 11 percent or less of all randomized patients contributed to these observations, and the report did not explain why some patients alive at 18 and 30 months were not re-assessed.

Gregor, Cull, Stephens, et al. (1997) assessed cognitive function at baseline, 6 months, and 1 and 2 years with a battery of optional measures including the National Adult Reading Test, Paced Auditory Serial Addition Task, Rey-Osterrieth Complex Figure Test, and Auditory Verbal Learning Test. Of 314 randomized patients, at least one test result was submitted for N=136 (52 controls, 84 PCI). Of these, baseline data were available for N=125, 6-month data for N=59 (of 106 assessable), one-year data for N=32 (of 54 assessable), and two-year data for N=9 (of 20 assessable). Each test showed evidence of new impairments at 6 months and 1 year in some patients free of impairments at baseline. However, investigators reported no evidence of sustained deterioration with time, and no notable differences between the PCI and control groups with respect to new cognitive deficits.

Gregor, Cull, Stephens, et al. (1997) also measured symptoms that affect QoL at the same intervals used for cognitive function, with the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale. Symptoms that showed the greatest deterioration from baseline to 6 months included tiredness, lack of energy, irritability, decreased sexual interest, shortness of breath, and cough. For each symptom, of those who reported themselves with no or mild symptoms at baseline, a larger proportion of controls than of those given PCI reported moderate or severe symptoms at 6 months. Based on these data, investigators concluded deterioration was worse in controls than in the PCI group.

Ohonoshi, Ueoka, Kawahara, et al. (1993) did not formally assess neuropsychological function or measure cognitive function or quality life. However, they reported that one of seven patients who survived more than two years after PCI developed symptoms of late central nervous system toxicity. These included memory impairment and gait ataxia at 30 months, with CT scan evidence of cortical atrophy. Ohonoshi, Ueoka, Kawahara, et al. (1993) did not report on late toxicity in the 4 control patients alive at 2 years.

Subsequent Study. Cao, Huang, and Tu (2000) reported the only eligible RCT of PCI versus no PCI omitted from the Cochrane review and meta-analysis (N = 47; 24 to PCI, 23 to control). Study arms were well-balanced and most patients had relatively favorable baseline characteristics: mean age, 55-56 (range 39–65), Karnofsky score $\geq$70, two females in each arm, all patients initially diagnosed with limited stage disease and in CR after chemotherapy plus TRTx. Chemotherapy regimens were either cyclophosphamide/doxorubicin/vincristine or etoposide plus carboplatin or cisplatin, with most patients also given lomustine. All patients received 40-66 Gy TRTx in 1.8-2 Gy fractions, given sequentially for most (17 controls, 18 PCI) and in alternating fashion for the rest (6 from each group). PCI began 11 to 58 days after achieving CR (mean, 33 days) at a mean dosage of 28.8 Gy (range, 25.2 to 30.6 Gy) in single daily fractions of 1.8 to 2 Gy, 5 days/week.

Cao, Huang, and Tu (2000) reported fewer cranial metastases at 3 years after irradiation in the arm given PCI (3.8 percent versus 28 percent, $p<0.05$). However, differences in survival at

one (85 percent versus 72 percent), two (73 percent versus 40 percent) or three (42 percent versus 32 percent) years were not statistically significant (median, 20 versus 8.3 months; log rank $p>0.05$). Acute reactions to PCI included mild nausea and dizziness, but frequencies were not reported. Late effects in 11 patients who survived $\geq$3 years included two with memory deficits and three with dizziness and lack of strength. Brain CT scans on 7 of the 11 survivors showed no structural abnormalities.

Conclusions

Evidence from an individual patient data Cochrane review and meta-analysis on seven RCTs (N=987) conducted by the PCI Overview Collaborative Group shows that PCI modestly but significantly improves survival of SCLC patients in CR after primary therapy. PCI increases the proportion alive at 3 years from 15.3 percent of controls to 20.7 percent of those randomized to PCI, an absolute increase of 5.4 percent. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial reported after the meta-analysis confirms effects of PCI on brain metastasis, and generally agrees with the modest effect on overall survival.

Subgroup analyses using individual patient data showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage or performance status at diagnosis, and whether or not TRTx is part of the induction regimen. Although effects of PCI on survival lacks statistical significance for nearly all these subgroups, it does not appear that any subgroup benefits more or less than others with respect to each of these covariates.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving CR may decrease the likelihood of brain metastasis. Patient gender also may interact with effects of PCI on survival. However, these hypotheses, derived from subgroup analyses, require formal testing in randomized, controlled trials.

Data on acute toxicities of PCI are scant, but those available suggest they are tolerable at the doses used in these trials (8–40 Gy in 1.8 to 3 Gy fractions). Evidence from two trials suggests neuropsychological and cognitive deficits and structural abnormalities on brain CT scans are relatively common among SCLC patients in CR after primary therapy. However, available evidence did not show greater deterioration of existing deficits or more frequent appearance of new abnormalities among the minority randomized to PCI who survive 1–2 years or more, than among the fewer controls with equivalent survival duration.

Key Question 6

Does the addition of positron emission tomography (PET) scanning improve the accuracy of staging for patients diagnosed with SCLC, over the use of other techniques, including CT and MRI, without PET?

Overview

Evidence of the effect of PET on health outcomes, such as overall survival or avoidance of unnecessary procedures, is of greatest interest to this review. RCTs were sought that compared outcomes of staging tests that included PET versus the same tests without PET in patients who had a confirmed diagnosis of SCLC. No such studies were found.

Single-arm studies with the following characteristics were sought: prospective design; reported on at least 20 patients undergoing imaging to stage SCLC; correlated 18-fluorodeoxyglucose (FDG) PET findings with findings from other imaging modalities and an appropriate reference standard; applied the reference standard to patients with and without metastasis to a given anatomic site (to permit computation of sensitivity and specificity); and reported at least one outcome of interest. Outcomes included: diagnostic and staging accuracy; patient management decisions, which may be altered by imaging results, duration of survival; disease-free survival and/or progression-free survival; quality of life; palliation of measurable symptoms; treatment-related adverse effects; objective response rates; and response durations. Studies were excluded if they did not report data needed to calculate diagnostic accuracy; or if they did not report separate diagnostic accuracy results for SCLC and NSCLC patients. Since the question posed here concerned the incremental value of PET relative to staging tests, the comparison of greatest interest is between results of conventional staging tests alone and conventional staging tests plus PET.

Due to the limited evidence available, the study selection criteria on prospective design and on appropriate reference standard were relaxed. Six studies reporting on a total of 277 patients (range: 20–120) are included in this review. Data from these studies primarily concerned diagnostic and staging accuracy. Characteristics of these studies are summarized in Summary Table 38 (sample selection) and Summary Table 39 (tests and reference standards). Four of the six studies were clearly prospective in design (Bradley, Dehdashti, Mintun et al., 2004; Brink, Schumacher, Mix et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003; Shen, Shiau, Wang, et al., 2002), while 1 study produced a mix of data collected prospectively and retrospectively (Blum, MacManus, Rischin, et al., 2004) and 1 study was of uncertain design (Schumacher, Brink, Mix, et al., 2001). Three studies enrolled consecutive series of patients (Blum, MacManus, Rischin, et al., 2004; Brink, Schumacher, Mix et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003). Three of the 6 studies provide staging accuracy data based on comparisons of conventional staging tests alone and conventional staging plus PET (Blum, MacManus, Rischin, et al., 2004; Bradley, Dehdashti, Mintun et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003). Three studies compared staging results of conventional tests alone and PET alone (Brink, Schumacher, Mix et al., 2004; Shen, Shiau, Wang, et al., 2002; Schumacher, Brink, Mix, et al., 2001).

Study quality was assessed as described in the Methods chapter, using the QUADAS tool (Whiting, Rutjes, Dinnes, et al., 2004). A major weakness of the included evidence is the uniformly poor quality of information reported about the reference standard. None of the 6 studies adequately described the execution of the reference standard and whether the reference standard correctly classifies the target condition. Without these details, the definition of a positive reference standard result is unclear. Thus the poor quality of information reported on reference standards undermines confidence in the estimates of sensitivity, specificity and staging accuracy that can be drawn from this literature.

Summary Table 38. Sample Selection: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	Design	Patient Selection	n	Age (yr)	Gender (%)	Stage Limited %	Stage Extensive %	Representative Sample?
Blum, MacManus, Rischin, et al., 2004	partially prospective, partially retrospective	proven SCLC underwent PET; consecutive patients; newly diagnosed-initial staging in 15, restaging in 21; PET based on review of all clinical data and was performed to guide clinical management;	36	med 64	M 66 F 33			Unclear
Bradley, Dehdashti, Mintun et al., 2004	prospective	newly diagnosed confirmed limited stage SCLC, completed standard staging procedures	24	mn 60 rng 33-90	M 44 F 56	87.5	12.5	Yes
Brink, Schumacher, Mix et al., 2004	prospective	consecutive patients with histologically confirmed SCLC examined with FDG-PET during primary staging	120	mn 60.8 sd 8.9	M 75 F 25	37	63	Unclear
Kamel, Zwahlen, Wyss, et al., 2003	prospective	consecutive patients with SCLC referred for whole-body FDG-PET; initial staging in 24 patients and restaging after therapy in 20 patients (both in 2)	42	mn 62 rng 45-83	M 64 F 36	62.5	37.5	Unclear
Shen, Shiau, Wang, et al., 2002	retrospective	histologically confirmed SCLC; KPS ≥ 60%; total serum bilirubin ≤ 2.0 mg/dL; serum creatinine ≤ 2.5 mg/dL; fasting blood sugar ≤ 150 mg/dL	25	mn 56 sd 7 rng 45-68	M 72 F 28	40	60	Unclear
Schumacher, Brink, Mix, et al., 2001	unclear	histologically proven SCLC, primary staging in 24, therapy follow-up in 4, both in 2; therapy was surgery, RTx and CTx (ACO, EPI-CO, VIP-E, VIC-E); all treatment stopped ≥1 mo before PET	30	mn 57 sd 13 rng 34-78	M 77 F 23	30	70	Unclear

Abbreviations table provided at the end of the Report.

Summary Table39. Test/Reference Standard Procedure and Interpretation: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	PET	Conventional Staging Tests	Reference Standard	PET: Ref Stand Blind?	Ref Stand: PET Blind?	Avoided Verification Bias
Blum, MacManus, Rischin, et al., 2004	≥ 4 hr fast; ± attenuation correction, qualitative interpretation, access to results of the previous imaging and clinical information	initial staging - high-quality CT of chest, upper abdomen, brain, usually bone scan; restaging after initial treatment - CT, bone scan, X-ray;	if discordant results, TP = site biopsy+; or site + only on PET with other progression < 6 mos of PET, no treatment; TN = site biopsy-; or conventional equivocal/negative site with no progression for ≥ 6 mos, no treatment	Unclear	Unclear	Unclear
Bradley, Dehdashti, Mintun et al., 2004	4-hr fast, 10-15 mCi FDG, 50 min delay ± attenuation correction, visual interpretation; 2 experienced nuclear physicians; first, independent, blinded to conventional, then observers reread with conventional, final consensus of blinded readings; also semiquantitative maximum standardized uptake value	history, physical exam, chest X-ray, chest CT, upper abdominal CT, bone scan, contrast-enhanced CT/MRI of brain; all conventional staging procedures completed ≤ 4 wk of PET	protocol-defined approaches for further evaluation or biopsy: PET+ intrapulmonary parenchymal metastases outside RTx portal, do biopsy; thin-cut CT- or US-guided FNA where feasible; liver PET+, do biopsy/FNA cytology; adrenal PET+, do biopsy; bone PET+, evaluate by appropriate imaging studies (X-ray, CT, MRI, repeat bone scan) or biopsy or bone scan/MRI if multiple bone metastases suspected	Unclear	Unclear	Unclear
Brink, Schumacher, Mix et al., 2004	12 hr fast, 5 MBq/kg FDG, 90 min delay; data corrected for dead time, decay, photon attenuation; whole-body PET performed after CT (mean 12 d, range 1-26 d), hard copy and computer workstation, 2 independent investigators blinded to other data; hot spot evaluation, consensus	conventional staging by history, physical exam, bronchoscopy, thoracic/abdominal contrast-enhanced CT, cranial CT/MRI in 91, bone biopsy in 84 (refused in 36)	histology in ~20%; available data; follow-up, committee of physicians (2 clinicians, 2 nuclear specialists) achieved reference standard diagnosis by consensus; when histologic results were unavailable, consensus based on sum of available data, including follow-up, non-validated results excluded from data analysis	Yes	Unclear	No
Kamel, Zwahlen, Wyss, et al., 2003	≥ 4 hr fast, 300-400 MBq FDG; 40-50 min delay; segmented or PET/CT fusion attenuation correction, pre-PET staging and post-PET staging were always performed independently; clinical information available, including CT	history, physical exam, blood tests, bronchoscopy, contrast-enhanced CT of chest, upper abdomen, bone scan, CT/MRI of brain in 9	when possible, biopsies or other imaging studies were performed to resolve discrepancies between modalities	Unclear	Unclear	Unclear

Abbreviations table provided at the end of the Report.

Summary Table39. Test/Reference Standard Procedure and Interpretation: Positron Emission Tomography for Staging of Small-Cell Lung Cancer (continued)

Study	PET	Conventional Staging Tests	Reference Standard	PET: Ref Stand Blind?	Ref Stand: PET Blind?	Avoided Verification Bias
Shen, Shiau, Wang, et al., 2002	6 hr fast; 10 mCi (370 MBq) FDG; 40-50 min delay, agreement of at least 2 of 3 experienced nuclear medicine specialists blind to clinical stage	within 2 wk of PET: history, physical exam, blood chemistry, chest X-ray $\pm$ chest CT/MRI, brain CT/MRI, abdominal CT/MRI $\pm$ hepatic US, pelvic CT/MRI, bone scan, bone marrow biopsy	final stage was verified by pathologic findings from thoracotomyy/mediastinoscopy. other imaging results, follow-up $\geq$ 1 yr	Unclear	Unclear	No
Schumacher, Brink, Mix, et al., 2001	12 hr fast; 5 MBq FDG/kg; 90 min delay attenuation correction ,hard copy and computer workstation; visual interpretation, 2 experienced independent blinded investigators; consensus; standardized uptake value > 4	within 2 wk before or after PET: CT/MRI of brain, thorax, abdomen carried out according to standard protocols, thin-section or contrast enhancement used if needed	if discrepancies between PET and other staging procedures found, selective additional examinations performed or existing images re-evaluated; in some cases, clinical follow-up proved/disproved inconsistent findings; confirmation necessary within 4 wk	Unclear	Unclear	No

Study Populations

The proportion of patients enrolled who had limited stage disease ranged from 30 percent to 87.5 percent in 5 studies; it could not be determined in the study by Blum, MacManus, Rischin, et al. (2004). Three studies (Blum, MacManus, Rischin, et al., 2004; Kamel, Zwahlen, Wyss, et al., 2003; Schumacher, Brink, Mix, et al., 2001) included samples mixed with those undergoing initial staging and other being restaged. In only one study was it clear that selection of patients was not based on referral for PET scanning (Bradley, Dehdashti, Mintun et al., 2004).

Diagnostic Accuracy

Three studies (Blum, MacManus, Rischin, et al., 2004; Brink, Schumacher, Mix et al., 2004; Shen, Shiau, Wang, et al., 2002; total N=181) reported diagnostic accuracy data (Summary Table 40). Results are presented below according to stage or site of disease.

Any Disease. The study by Blum, MacManus, Rischin, et al. (2004) was the only one that reported diagnostic accuracy with reference to any disease. These investigators only included data on sensitivity in 36 patients, which they estimated at 100 percent for PET. This study does not address whether there was additional value to adding PET to staging, information about extent of disease was not reported.

Lymph Nodes. Using the patient (n=118) as the unit of analysis, Brink, Schumacher, Mix et al. (2004) found that PET had a sensitivity of 100 percent for detecting lymph node metastasis, compared with 69.8 percent for conventional staging. PET specificity was 98.5 percent, while it was 93.8 percent for conventional staging. The study by Shen, Shiau, Wang, et al. (2002) also used a patient-based analysis, but grouped lymph nodes into regions. Few patients provided data on negative nodes, so specificity was not reported. Shen, Shiau, Wang, et al. (2002) did not provide separate sensitivity data for PET and conventional imaging. PET was found to be 100 percent sensitive in each of 3 lymph regions: in 9 patients with mediastinal or hilar lymph metastases; in 7 patients with ipsilateral supraclavicular lymph metastases; and in 5 patients with contralateral supraclavicular lymph metastases. There were 2 PET false positives in mediastinal/hilar lymph nodes.

Other Regional Sites. Shen, Shiau, Wang, et al. (2002) reported that sensitivity for ipsilateral lung foci was 100 percent in 2 patients.

Summary Table 40. Diagnostic Accuracy Results: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	Test	Focus	n	TP	FN	FP	TN	Prev	Sens	Sens 95% CIL	Sens 95% CIU	Spec	Spec 95% CIL	Spec 95% CIU	PPV	NPV	DA
Blum, MacManus, Rischin, et al., 2004	PET	any disease	36	36	0				100%	90.3%	100%						
Bradley, Dehdashti, Mintun et al., 2004	PET	Any disease	24	24	0	1	0		100%	85.5%	100%						
Brink, Schumacher, Mix et al., 2004	PET	LNs	118	53	0	1	64	44.9%	100%	93.3%	100%	98.5%	91.7%	100%	98.1%	100%	99.2%
	Conv		118	37	16	4	61	44.9%	69.8%	55.7%	81.7%	93.8%	85.0%	98.3%	90.2%	79.2%	83.1%
	PET	dist, non-brain	70	45	1	2	22	65.7%	97.8%	88.5%	99.9%	91.7%	73.0%	99.0%	95.7%	95.7%	95.7%
	Conv		70	38	8	5	19	65.7%	82.6%	68.6%	92.2%	79.2%	57.8%	92.9%	88.4%	70.4%	81.4%
	PET	brain	91	6	7	2	76	14.3%	46.2%	19.2%	74.9%	97.4%	91.0%	99.7%	75.0%	91.6%	90.1%
	Conv		91	13	0	0	78	14.3%	100%	75.3%	100%	100%	95.4%	100%	100%	100%	100%
Kamel, Zwahlen, Wyss, et al., 2003																	
Shen, Shiau, Wang, et al., 2002	PET	regl mets	18	20	0	2	0		100%	83.2%	100%						
		MD/HL LNs	9	9	0	2	0		100%	66.4%	100%						
		ips SC LNs	7	7	0	0	0		100%	59.0%	100%						
		ips lung	2	2	0	0	0		100%	15.8%	100%						
		distant	24	23	1	1	0		95.8%	78.9%	100%						
		contr SC LNs	5	5	0	0	0		100%	47.8%	100%						
		contr lung	3	3	0	1	0		100%	29.2%	100%						
		liver	3	3	0	0	0		100%	29.2%	100%						
		bone/marrow	6	6	0	0	0		100%	54.1%	100%						
		brain	2	1	1	0	0		50.0%	1.3%	99%						
		adrenal	2	2	0	0	0		100%	15.8%	100%						
		other extrathoracic	3	3	0	0	0		100%	29.2%	100%						
Schumacher, Brink, Mix, et al., 2001																	

Abbreviations table available at the end of the Report.

Distant Sites, Non-Brain. Among 70 patients, Brink, Schumacher, Mix et al. (2004) found that PET's sensitivity for distant non-brain sites was 97.8 percent, compared with 82.6 percent for conventional staging. Specificity was 91.7 percent for PET and 79.2 percent for conventional staging. In the Shen, Shiau, Wang, et al. (2002) study, PET had 100 percent sensitivity in 19 patients. Sites in this study included contralateral lung (1 false positive), liver, bone/marrow, adrenal and other extrathoracic.

Brain Metastases. In the Brink, Schumacher, Mix et al. (2004) study, PET's sensitivity was 46.2 percent, compared with 100 percent for conventional staging, among 13 patients. Specificities were 97.4 percent for PET and 100 percent for conventional staging. Shen, Shiau, Wang, et al. (2002) included 2 patients with brain metastases and PET detected 1 (50 percent sensitivity).

Staging Accuracy

All 6 studies reported on instances in which PET correctly upstaged disease among those undergoing initial staging (Table 41). The proportions were: 3 of 15 (20 percent) in Blum, MacManus, Rischin, et al. (2004); 1 of 24 (4.2 percent) in Bradley, Dehdashti, Mintun et al. (2004); 10 of 120 (8.3 percent) in Brink, Schumacher, Mix et al. (2004); 3 of 24 (12.5 percent) in Kamel, Zwahlen, Wyss, et al. (2003); 1 of 25 (4 percent) in Shen, Shiau, Wang, et al. (2002); and 5 of 30 (19.2 percent) in Schumacher, Brink, Mix, et al. (2001). Three studies mentioned examples of PET correctly downstaging disease. Brink, Schumacher, Mix et al. (2004) found 3 cases in 24 (12.5 percent), Kamel, Zwahlen, Wyss, et al. (2003) observed 1 in 24 (4.2 percent) and Shen, Shiau, Wang, et al. (2002) saw 1 in 25 (4 percent). Among patients being restaged, Schumacher, Brink, Mix, et al. (2001) reported that PET correctly upstaged disease in 1 of 6 patients (16.7 percent).

In two studies, PET was found to correctly rule in disease at various sites. In the Bradley, Dehdashti, Mintun et al. (2004) study the site was lung in 1 patient (4.2 percent) and regional lymph nodes in 6 (25 percent). In the Kamel, Zwahlen, Wyss, et al. (2003) study, the sites were: visceral/soft tissue in 1 patient undergoing initial staging (4.2 percent); lung in 1 restaged patient (5 percent); and breast/axilla in 1 restaged patient. PET was shown to correctly rule out disease in selected sites in the Kamel, Zwahlen, Wyss, et al. (2003)study, including: adrenal gland in 1 patient who was initially staged (4.2 percent); bone in 1 who was restaged (5 percent); and lymph node in 2 restaged patients (10 percent).

Only Kamel, Zwahlen, Wyss, et al. (2003) and Shen, Shiau, Wang, et al. (2002) reported the frequency of incorrect staging by PET; it is unclear from the other studies how often restaging by PET was incorrect. Both Kamel, Zwahlen, Wyss, et al. (2003) and Shen, Shiau, Wang, et al. (2002) found no cases incorrectly upstaged or downstaged by PET at initial staging, but Kamel, Zwahlen, Wyss, et al. (2003)reported 1 case being restaged that was incorrectly upstaged.

Changes in Patient Management

Four studies reported on instances in which patient management was changed based on PET results. The total proportions were: 41.7 percent in Blum, MacManus, Rischin, et al. (2004); 58.3 percent in Brink, Schumacher, Mix et al. (2004); 29.2 percent in Bradley, Dehdashti, Mintun, et al. (2004) and 28.6 percent in Kamel, Zwahlen, Wyss, et al. (2003). Specific changes

Summary Table41. Staging Accuracy Results/Changes in Patient Management: Positron Emission Tomography for Staging of Small-Cell Lung Cancer

Study	Test	Use	PET Correctly Changed Stage	#	%	PET Ruled-in (R/I) or Ruled-out (R/O) Metastases	Site	#	%	PET Missed Metastases	Site	#	%	PET Changed Patient Management	#	%	Changes
Blum, MacManus, Rischin, et al., 2004	PET	staging	up	3	20										4	26.7	forgone RTx for ED
															1	6.7	ED, received palliative CTx/RTx
															2	13.3	RTx target volume changed
															3	12	PCI omitted
															3	12	PCI selected
															2	8	forgone CTx, observation for NED
Bradley, Dehdashti, Mintun et al., 2004	PET	staging	up	1	4.2	R/I	lung	1	4.2						7	29.2	RTx target volume changed
						R/I	regl LNs	6	25								
Brink, Schumacher, Mix et al., 2004	PET	staging	up	10	8.3						brain	1	0.8		10	8.3	forgone RTx for ED
			down	3	2.5										3	2.5	selected CTx/RTx
															1	0.8	missed brain metastasis, affected treatment
Kamel, Zwahlen, Wyss, et al., 2003	PET	staging	up	3	12.5	R/I	visceral/ soft tissue	1	4.2		brain	2	8.3		12	29	
			down	1	4.2	R/O	adrenal	1	4.2						9	37	forgone RTx for ED (3)
																	altered radiation field (5)
											LN	1	5				selected surgery (1)
		restaging				R/I	lung	1	5						3	15	CTx reinstituted (1)
						R/I	breast/ axilla	1	5								CTx discontinued (2)
						R/O	LN	2	10								
						R/O	bone	1	5								
Shen, Shiau, Wang, et al., 2002	PET	staging	up	1	4												
			down	1	4												
Schumacher, Brink, Mix, et al., 2001	PET	staging	up	5	19.2												
		restaging	up	1	16.7												

included the following: forgoing of RTx for extensive disease; palliative CTx/RTx selected for extensive disease; change in RTx target volume; PCI selected; PCI omitted; forgoing of CTx for no evidence of disease; CTx/RTx selected for limited disease; surgery selected; CTx reinstituted; and CTx discontinued.

Study Quality. The quality assessment tool used for Key Question 6 includes 14 items, 8 of which focus on the reference standard (Appendix Table 4G).* A reference standard is the basis for estimating sensitivity and specificity. As noted, the quality of information about the reference standard was uniformly poor, undermining confidence in estimates of sensitivity and specificity. The ratings of study quality can be seen in Summary Table 42.

Given 14 items in the instrument and 6 studies, there were 84 data points, among which 51 percent were rated as unclear, underlining the prevalence of poor reporting in these articles.

In only 1 study (Bradley, Dehdashti, Mintun et al., 2004) was it clear if the sample was representative of population of interest. Conventional staging suggested that patients in the Bradley, Dehdashti, Mintun et al. (2004) study had limited disease, so PET was used to determine if any patients were understaged. In all of the other 5 studies, it is unclear why patients were referred for PET and no study clearly stated that an intact group of patients newly diagnosed with SCLC were enrolled. Selection criteria were clear only in the Bradley, Dehdashti, Mintun et al. (2004) study. For all other studies, criteria were unclear. Articles by Brink, Schumacher, Mix et al. (2004) and Shen, Shiau, Wang, et al. (2002) suggest that PET results influenced performance of the reference standard. In the other 4 studies, it is unclear if PET results influenced performance of the reference standard. The Bradley, Dehdashti, Mintun et al. (2004) study did not incorporate PET into the reference standard, while in all other studies, it was unclear whether PET and the reference standard were independent. Only the Bradley, Dehdashti, Mintun et al. (2004) study stated that PET was interpreted blind to the reference standard; all others were unclear.

Conclusions

Six studies reporting on a total of 277 patients (range 20-120) provided data on the diagnostic accuracy of PET in SCLC. The evidence suggests that, except for detection of brain metastases, the PET added to conventional staging is more sensitive in detecting disease than conventional staging alone. Upstaging was reported in 4–20 percent of patients and downstaging in 4–13 percent of patients. Three studies reported very high occurrence of patient management changes that were attributed to PET (29–58 percent).

However, the quality of these studies is consistently poor and insufficient detail in reporting was the norm. There is such a high degree of uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. Although these studies report that PET has correctly upstaged or downstaged the extent of disease, the frequency of incorrect changes in stage attributable to PET is unknown due to incomplete reporting. It is not possible to determine the frequency with which management changes, based on PET results, were actually beneficial or harmful.

Thus it is not possible from the limited and poor quality evidence that is available to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

Summary Table 42. Ratings of Study Quality for Key Question 6

Item	Blum	Bradley	Brink	Kamel	Shen	Schumacher
Representative sample?	?	+	?	?	?	?
Clear patient selection criteria?	?	+	?	?	?	?
Correct reference standard classification of target?	?	?	?	?	?	?
Short period between test and reference standard?	?	?	?	?	?	?
Random/whole sample received reference standard?	+	+	+	+	+	+
Received reference standard regardless of test results?	?	?	-	?	-	-
Reference standard independent of test?	?	+	+	?	?	?
Test execution sufficiently described?	+	+	+	+	-	+
Reference standard execution sufficiently described?	-	-	-	-	-	-
Test interpreted blind to reference standard?	?	?	+	?	?	?
Reference standard interpreted blind to test?	?	?	?	?	?	?
Clinical data available?	+	+/-	-	+	-	-
Uninterpretable/indeterminate results?	-	-	-	-	-	+
Withdrawals explained?	+	+	+	+	+	+

Key Question 7

What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

Overview

Two types of studies were sought: RCTs that compared alternative chemotherapy regimens for mixed small cell/non-small cell cancers; and phase II prospective trials reporting on at least 25 patients treated with a single regimen that reported at least one health outcome of interest. Health outcomes included: duration of survival; disease-free survival and/or progression-free

survival; quality of life; treatment-related adverse effects; objective tumor response rates; and response durations.

Results

No studies meet selection criteria for this question. Very few references from the literature search represented studies of any kind that included patients with mixed histology. Several studies are described below, along with reasons for exclusion.

- The single-arm study by Ruffini, Rena, Oliaro, et al. (2002) was excluded because it could not be confirmed as a prospective phase II multicenter trial. It was clearly conducted as a single-center case series of patients with mixed histologic pattern who underwent surgery. The article does not mention that it was prospective and is likely to be retrospective. Between 1993 and 1999, 1158 patients underwent surgery for lung tumors. Among these were 59 patients with a mixed histologic pattern, separated into 3 main subgroups: 1) adenosquamous carcinoma, n=33, 2) combined neuroendocrine + non-neuroendocrine carcinoma (NNEC), n=21, and 3) biphasic tumors, n=5. The second subgroup included 14 patients with SCLC: 10 who had SCLC + squamous cell carcinoma and 4 who had SCLC + adenocarcinoma. The article provides survival data for 19 of the patients in the second subgroup.

- SmytheEstrera, Swisher, et al. (2001) was excluded because it was not prospective or multicenter and it did not enroll the minimum of 25 patients. These authors reported a single-center retrospective study of 11 patients who underwent surgery for NSCLC after treatment for SCLC. The study period spanned 1978 to 1998. Survival results for the mixed histology patients were compared with 3 control groups: 1) 23 patients with stage I NSCLC undergoing any resection; 2) 46 patients with stage I NSCLC undergoing wedge resection; and 3) 17 patients undergoing wedge resection who had NSCLC and a prior malignancy.

- A subset of patients with mixed histology from an RCT is discussed by Aisner, Finkelstein, Ettinger, et al. (1990). This study is excluded because outcomes are not presented according to treatment group. Patients with extensive stage SCLC received one of 2 induction chemotherapy regimens and complete responders were further randomized to maintenance chemotherapy or observation after whole brain irradiation. A pathologist reviewed the tumor specimens according to a revised classification scheme that includes a variant-morphology category characterized as the small-cell/large-cell (SC/LC) subtype. An initial review of 577 patients identified 24 with the SC/LC subtype. Subsequent review with a second pathologist confirmed only 11 patients in this category. Of these 11 patients, 3 achieved a complete response and 4 achieved a partial response.

- The paper by Johnson, Ihde, Bunn, et al. (1985) is excluded because it presents outcome data for only a single patient with mixed histology. This article summarized data from a series of intramural NCI clinical trials that included 252 patients with newly diagnosed SCLC. Of these, 19 patients were of SC/LC subtype. The article focuses on 19 patients

who achieved long-term survival (≥30 months). Only 1 SC/LC patient was a member of this group.

Conclusions

No studies meet selection criteria for this question. Very few references from the literature search represented studies of any kind that included patients with mixed histology. No conclusions can be drawn on outcomes of treatment for patients with mixed small cell/non-small cell lung cancers.

Key Question 8

What is the role of surgery and what is its impact on survival in patients with very early stage SCLC? How do available studies define very early stage SCLC?

Overview

Very early limited SCLC is defined as no preoperative evidence of involved nodes (clinically N0). In a retrospective analysis of 264 limited stage SCLC patients treated with chemotherapy and radiation from 1976 through 1985, Shepherd, Ginsberg, Haddad et al. (1993) found significantly (p=0.02) better survival for patients clinically staged with negative mediastinal nodes, compared to those with positive mediastinal nodes and also to those with pneumonic consolidation, pleural effusion, atelectasis, or supraclavicular adenopathy. About half the patients classified node negative underwent mediastinoscopy and half were staged by thoracic CT or X-ray only. Unfortunately, retrospective analyses of resected SCLC patients show that clinical (preoperative) staging frequently underestimates pathologic stage (Shepherd, Ginsberg, Patterson et al. 1989; Shepherd, Ginsberg, Feld et al. 1991; Inoue, Miyoshi, Yasumitsu et al. 2000) and inadequately separates limited stage patients by prognosis (Waddell and Shepherd, 2004). Moreover, detection of involved nodes depends on the methods used for staging.

For this question, randomized, controlled trials that compared surgery to no surgery in patients with very early limited SCLC were sought. Two randomized, controlled trials were identified (Lad, Piantadosi, Thomas, et al., 1994; Liao, Zhao, Zhou, et al., 1995), but each had serious limitations for purposes of this review (Summary Table 43). First, neither used platinum based chemotherapy, and thus had limited relevance to contemporary treatment settings. Second, neither RCT studied a homogeneous group with respect to nodal status at randomization (Summary Table 44). The larger RCT (Lad, Piantadosi, Thomas, et al., 1994; N=146) included patients with involved mediastinal nodes, and it is uncertain whether Liao, Zhao, Zhou, et al. (1995; N=40) excluded such patients. Neither study reported outcomes separately for a subgroup without nodal involvement. Since relevant RCT data were lacking, we also sought data from non-randomized comparative studies, both prospective and retrospective (see Summary Table 43 and Appendix Tables 8A-D).[*] Eight studies were identified:

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

- one case-control study (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005);

- a prospective study of surgery with a comparison group of surgical candidates who did not undergo thoracotomy (Shepherd, Ginsberg, Patterson, et al. 1989);

- four retrospective analyses (Namikawa, Den, Kimura, et al., 1994; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991; Friess, McCracken, Troxell, et al., 1985; Osterlind, Hansen, Hansen, et al., 1985); and

- two registry analyses (Rostad, Naalsund, Jacobsen, et al., 2004; George, Fitzgerald, Brown, et al., 1986).

These studies had similar limitations with respect to treatment regimens and included patients (Summary Tables 43 and 45). Three studies used platinum-based regimens (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005; Shepherd, Ginsberg, Patterson, et al. 1989; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991), but not for all included patients. Only the Rostad, Naalsund, Jacobsen, et al. (2004) registry analysis restricted their study population to patients with very early limited stage disease (N0 patients clinically staged Ia or Ib).

Summary Table 43. Studies Comparing Surgery versus No Surgery for Early Limited Stage SCLC

Study	N evaluated		Pt?	ChemoTx regimen	TRTx?	PCI?	resections		response status[3]	study type	# centers	quality rating
	+surg	-surg					types[1]	timing[2]				
Lad, Piantadosi, Thomas, et al., 1994	70	76	no	CAV	all	all	54 c, 4 p, 12 T	after	40% CR 60% PR	RCT	multi	fair
Liao, Zhao, Zhou, et al., 1995	20	20	no	IMAV	-surg only	NR	NR	mid	70-80% CR	RCT	one	poor
Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005	67	67	some[4]	various	58% of -surg	34% of +surg	30 P 37 L	before	not relevant	case-control	one	poor
Shepherd, Ginsberg, Patterson et al. 1989	38	19	~5%	various	all	all	8 P, 25 L 5 T	after	45% CR 50% PR	non-random.	multi	fair
Namikawa, Den, Kimura, et al., 1994	58	43	NR	NR	NR	NR	NR	NR	?	retro-spect.	one	poor
Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991	36	45	~33%	various	all	NR	4 P, 27 L 5 B	19 before 17 after	24% CR 59% CR	retro-spect.	one	poor
Friess, McCracken, Troxell, et al., 1985	15	246	no	COMF or CAV	all	all	3 P 12L	before	not relevant	retro-spect.	multi	fair
Osterlind, Hansen, Hansen, et al., 1985	33	46	no	CCM±V±A±E	33% each	7-12%	11c, 13p 9<p	before	not relevant	retro-spect.	two	fair
Rostad, Naalsund, Jacobsen, et al., 2004	29	96	NR	NR	NR	NR	3P, 15L 3B, 5<p	before	not relevant	registry	multi	poor
George, Fitzgerald, Brown, et al., 1986	13	88	no	various	NR	NR	NR	before	not relevant	registry	multi	poor

[1] resection types: c=complete; p=partial; <p=less than a partial resection; T=thoracotomy only (open and close); P=pneumonectomy; L=lobectomy; B=bilobectomy; [2] resection timing: after = after all chemotherapy cycles; before = before any chemotherapy; mid = between cycles; [3] at the time of randomization or resection; [4] proportion treated with platinum not reported.

Summary Table44. Sample and Methods: Surgery versus No Surgery for Very Early Limited Stage Disease

Study	N	Age	% Female	% Performance Status	+Surg: Type of Resections	CTX Regimen	RTx Regimen
Lad et al. 1994 RCT multi-center late 1983 - 10/1989	Total 146 +surg 70 -surg 76	md (rng) 59 (35-72); arms pooled, but "well matched"	35 arms pooled but "well matched"	82% with KPS ≥90 arms pooled but "well matched"	54 complete 4 partial 12 open & close	CAV same	Dose / Schedule / PCI? 50 Gy / 25 x 2 Gy / 30 Gy 15 x 2 Gy
Liao et al. 1995 single center RCT (Shanghai) 1/90-12/91	Total 40 +surg 20 -surg 20	mn (rng) 50 (33-74) 54 (31-66)	10 10	NOT REPORTED	not reported	same for all: ifosfamide, Mesna, doxorubicin, vincristine	Dose / Schedule / PCI? only for -surg arm; dose, schedule not reported / not reported
Badzio et al. 2004, 2005; pair-matched case/control one center 1984-96	Total 134 +surg 67 -surg 67 in CR 23	mn (rng) 57 (29-70) 54 (36-71) (p=0.03)	15 22 (p=0.27)	0 1 2 3 60 36 4 58 33 9 WHO	30 pneumonectomy; 37 lobectomy	CAV, CDE, PE or MCCC/CAV/VI CCMV or ACOM	Dose / Schedule / PCI? 30-50 Gy / 10, 20, or 25 fracs; n=39 -surg only / n=23, +surg only; dose, fractionation not reported
Shepherd et al. 1989; adjuv. surgery post chemoTx; non-randomized multi-center	Total 57 +surg 38 -surg 19	md (rng) 60 (39-77) 59 (44-75)	32 47	NOT REPORTED	8 pneumonectomy; 25 lobectomy; 5 thoracotomy only	CAV±etoposide or PE	Dose / Schedule / PCI? 25-35 Gy / 10-20 fracs / 20 Gy in 5 fracs same
Namikawa et al. 1994 retrospective series; single center 1960-86	Total 101 +surg 58 -surg 43	NOT REPORTED	NOT REPORTED	NOT REPORTED	NOT REPORTED	NOT REPORTED	Dose / Schedule / PCI? NOT REPORTED
Hara et al. 1991 retrospective series; single center 1972-89	Total 81 +surg 36 -surg 45	mn (rng) 64 (44-76) 63 (45-83)	17 16	0 1 2 3 50 44 6 18 78 4 ECOG	4 pneumonectomy; 27 lobectomy; 5 bilobectomy	various regimens same	Dose / Schedule / PCI? 30-70 Gy (mn 46 Gy) / 1.4-2 Gy, 25-36 fracs, 1/d / NOT REPORTED
Friess et al. 1985 retrospective analysis of SWOG 7628 patients; 1977-9	Total 261 +surg 15 -surg 246	NOT REPORTED	NOT REPORTED	NOT REPORTED	3 pneumonectomy; 12 lobectomy	4 different regimens	Dose / Schedule / PCI? 2 x 30 Gy ± 15 Gy boost / NOT REPORTED / dose, fracs not reported

Summary Table44. Sample and Methods: Surgery versus No Surgery for Very Early Limited Stage Disease (continued)

Study	N	Age	% Female	% Performance Status	+Surg: Type of Resections	CTX Regimen	RTx Regimen
Osterlind et al. 1985; retrospective analysis of patients from 6 trials, 2 Danish institutions, 3/73-9/81	Total 79 +surg 33 -surg 46	mn (sd) 55 (±8) 60 (±6)	 18 28	AJC[1] 0-1 2 3-4 83 17 0 91 6 3	11 complete, 13 partial, 9 <partial resections	CCM ± vincristine ± (doxorubicin + etoposide)	Dose Schedule PCI? 33% of each group, but dose, schedule not reported 12% 7% but regimen details not reported
Rostad et al. 2004 registry analysis all cases in Norway, 1993-9	Total 125 +surg 29 -surg 96	"no age difference" between groups	NOT REPORTED	NOT REPORTED	3 pneumonectomy; 15 lobectomy; 3 bilobectomy; 5 minor resection	NOT REPORTED	Dose Schedule PCI? no details provided not specified
George et al. 1986 registry analysis all cases in Rochester, NY 1975-81	Total 101 +surg 13 -surg 88	14% 31-50 29% 51-60 38% 61-70 19% ≥71 (groups pooled)	35 (groups pooled)	NOT REPORTED	NOT REPORTED	CCM, CMVP, CC, or CAV same	Dose Schedule PCI? no details provided not specified

[1] American Joint Committee for Cancer Staging, 1979
Abbreviations table provided at the end of this Report.

Summary Table 45. Eligibility criteria and staging procedures used in studies of surgery for very early limited stage SCLC

Study	eligibility criteria for inclusion by clinical staging evaluation											staging procedures utilized						
	diagnosis before thoracotomy?	solitary peripheral nodules?	T2 tumors	T3 tumors	involved mediastinal nodes	involved supraclavic-ular nodes	involved hilar nodes	pleural effusion	pericardial effusion	superior vena cava syndrome	stage II disease	stage III disease	chest imaging	abdominal imaging	brain imaging	bone imaging	bone marrow evaluation	bronchos-copy	medistin-oscopy
Lad et al., 1994	yes	no	yes	yes	yes	?	?	?	no	no	yes	yes	?	yes; method unknown	CT	yes; method unknown	yes	yes	?
Liao et al., 1995	yes	no	yes	yes	?	?	?	?	?	?	yes	yes	CT	CT & US	CT	RNS	yes	?	?
Badzio et al., 2004	no	?	yes	no	yes	no	?	no	?	?	yes	yes	CT	CT or US	CT	RNS	no	yes	not routinely
Shepherd et al., 1989	yes	no	yes	yes if N0	yes	?	?	?	?	?	yes	yes	some CT	RNS	CT or RNS	RNS	yes	?	yes if no CT
Namikawa et al., 1994	most	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Hara et al., 1991	yes	?	yes	?	yes	?	?	?	?	?	yes	yes	CT	CT or RNS	CT or RNS	CT or RNS	yes	yes	?
Friess et al., 1985	yes	?	?	?	yes	yes	?	?	?	?	?	?	X ray	RNS	RNS	RNS	yes	?	?
Osterlind et al., 1985	yes	?	?	?	no	no	no	?	?	?	no	no	?	?	?	?	yes	in most	in most
Rostad et al., 2004	?	?	yes	no	no	no	no	?	?	?	no	no	CT for some	?	?	?	?	?	?
George et al., 1986	?	?	yes	yes	yes	yes	yes	no	?	?	yes	yes	CT for some	CT, US or RNS in 75%	CT or RNS in 77%	?	yes in 58%	?	?

yes=eligible for inclusion, or procedure was used for staging ; no=not eligible for inclusion or not used or evaluated for staging ; ?= cannot be determined from information in published report;
Abbreviations table provided at the end of this Report.

Summary Table 46. Survival Outcomes: Surgery versus No Surgery for Very Early Limited Stage Disease

Study	N	OS Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)	TTP Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)
Lad et al., 1994	+surg 70	15.4	~60	20	~20	~20	~20						
multi-center RCT	-surg 76	18.6	~65	20	~20	~20	~20						
									NOT REPORTED				
	Difference	-3.2	-5	0									
		log rank p=0.78											
Liao et al., 1995 single-center RCT (Shanghai) 1/90-12/91	+surg 20		79	52	24								
	-surg 20		63	18	18								
									NOT REPORTED				
	Difference		16	34	6								
		(log rank p=0.12; t-test at 2 yr, p<0.05)											
Badzio et al., 2004, 2005	+surg 67	22.3	70	43	~35	~30	27	20.9					
									(time to relapse or progression)				
	-surg 67	11.2	45	17	~12	~4	4	7					
single center	(in CR 23)	(22)		(36)			(26)						
case-control	Difference	11.1	25	26	~23	~26	23	13.9					
		p < 0.001; HR = 0.42; 95% CI: 0.28, 0.61						p < 0.001					
Shepherd et al., 1989	+surg 38	22.8	~63	~47	~36	~36	36						
	-surg 19	11.8	~48	~10	~10	~10							
non-randomized multi-center									NOT REPORTED				
	Difference	10	~15	~37	~26	~26							
		p = 0.049											
Namikawa et al., 1994	resected 43	8.1											
	explored[1] 15	5.1											
single center case series	-surg 43	5.2							NOT REPORTED				
	Difference	2.9 (statistical test result not reported)											
Hara et al., 1991	+surg 36	33					38						
single center case series	-surg[2]: CR 19	24.5					21						
	PR 20	12.5					0		NOT REPORTED				
	Difference	8.5 (+surg – CR)											
		20.5 (+surg – PR) (statistical test result not reported)											

[1] patients found intra-operatively to have unresectable disease

[2] results for unresected patients reported separately for complete (CR) and partial (PR) responders to chemotherapy ± TRTx

Summary Table 46. Survival Outcomes: Surgery versus No Surgery for Very Early Limited Stage Disease (continued)

Study	N	OS Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)	TTP Med (mos)	1 yr	2 yr	3 yr	4 yr	5 yr (%)
Friess et al., 1985	+surg 15	25		44									
	-surg 246	10.5 (p=0.0037)		13.7 (p<0.05)									
4-arm RCT	33[3]	10 (range, 1-46+; p=0.03)						NOT REPORTED					
subgroup analysis	Difference	15		30.3									
Osterlind et al., 1985; retrospec-	+surg 33		~37	~16	~14	~14		DFS:	15% at 1.5 yr, 12% at 2 yr				
tive analysis, patients from 6	-surg 46		~50	~16	~10	~8			15% at 1.5 yr, 13% at 2 yr				
trials, 2 Danish	Difference		~(-13)	0	~4	~6			none				
institutions, 3/73-9/81			(p=0.35 by life table analysis)										
Rostad et al., 2004	+surg 29						44.9 (95% CI: 23.9, 65.9)						
	-surg 96						11.3 (95% CI: 4.2, 18.4)						
registry analysis	Difference						33.6	NOT REPORTED					
George et al., 1986	+surg 13	30.8	~70	~56	~46	~40	~40						
	-surg (all) 88	12.4											
registry analysis	CTx 43	11.9	~43	~15	~10	~4	0	NOT REPORTED					
	RTx 20	13.4	~58	~20	~20	~20	18						
	both 25	14.1											
	Difference	18.4 [+surg – (all -surg)]; (p=0.009 versus all –surg)											

[3] subgroup of unresected patients selected for "similar initial presentation" as those resected

Summary Table 47. Adverse Events: Surgery versus No Surgery for Very Early Limited Stage Disease

Toxicity Type	Study	Severity or Grade	Early n	%	Late n	%	p	Not Reporting
Treatment-related or operative mortality	Lad 1994		70	2.9	76	NR		Badzio 2004; Namikawa 1994; Friess 1985; Osterlind 1985; Rostad 2004
	Liao 1995		20	0	20	0		
	Shepherd[1] 1989		38	0	19	NR[1]		
	Hara 1991		36	0	45	NR		
	George 1986		13	0	88	1[2]		

[1] 2 of 72 patients (3%) died after the first course of chemotherapy.
[2] given chemotherapy plus TRTx

Only Shepherd, Ginsberg, Patterson, et al. (1989) reported post-operative complications other than mortality. Among 38 resected patients, they observed:

1 severe bronchospasm (2.6%)
1 prolonged atelectasis (2.6%)
1 pulmonary edema (2.6%)
2 transient arrhythmias (5.3%)
1 assisted ventilation for 6 weeks (2.6%)

Randomized, Controlled Trials

Interventions. Although two RCTs compared outcomes for limited stage SCLC patients managed with versus without surgery, neither trial fully adhered to a contemporary management strategy (Lad, Piantadosi, Thomas, et al., 1994; Liao, Zhao, Zhou, et al., 1995; see Table 43, Table 44, Appendix Tables 8A-D). Only the Lad, Piantadosi, Thomas, et al., (1994) trial used TRTx (and PCI) for all patients, while the Liao, Zhao, Zhou, et al. (1995) trial only gave TRTx to those randomized to no surgery. Patients in the Lad, Piantadosi, Thomas, et al. (1994) trial received TRTx sequentially after completing chemotherapy (and post-operative recovery if randomized to surgery). The Liao, Zhao, Zhou, et al. (1995) trial scheduled operations (and TRTx for the other arm) after chemotherapy cycles 2 or 3 (of up to 7). Each treatment regimen lacked platinum.

Study Populations. Published information suggests that neither RCT studied a homogeneous group of patients with respect to nodal status at randomization (Table 44). Lad, Piantadosi, Thomas, et al. (1994) randomized limited stage patients in CR or PR after five cycles of induction (neoadjuvant) chemotherapy. They did not report nodal status by clinical staging after chemotherapy for either arm. However, of 70 patients randomized to surgery, 15 were clinically N0 at registration (before induction), and 16 were pathologically N0 after resection. Ninety to 95 percent of those Liao, Zhao, Zhou, et al. (1995) randomized were in stage III. They reported 70–80 percent in CR, but it is uncertain when in the course of therapy these remissions were achieved. Liao, Zhao, Zhou, et al. (1995) also did not report nodal status before chemotherapy or after cycles 2-3, when surgery or radiation therapy took place.

Neither trial required mediastinoscopy or other invasive staging. Noninvasive staging was inadequately described in both RCTs.

Results. By log rank analysis, neither RCT found a statistically significant difference between Kaplan-Meier survival curves for those managed with versus without surgery (Lad, Piantadosi, Thomas, et al., 1994, $p=0.78$; Liao, Zhao, Zhou, et al., 1995, $p=0.12$; see Table 46, Appendix Table 8E). However, Liao, Zhao, Zhou, et al. (1995) reported a significant difference in percent survival at two years that favored the arm randomized to surgery (52 percent versus 18 percent; $p<0.05$ by t-test). Neither RCT reported time to relapse or progression, disease-free survival, or quality of life outcomes.

Nonrandomized Comparisons

Interventions. Only three of the eight studies reported that all patients received TRTx (Shepherd, Ginsberg, Patterson, et al., 1989; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991; Friess, McCracken, Troxell, et al., 1985), and only two used PCI (Shepherd, Ginsberg, Patterson, et al. 1989; Friess, McCracken, Troxell, et al., 1985). Only the Shepherd, Ginsberg, Patterson, et al. (1989) study resected patients after chemotherapy was completed. Three studies used platinum-based regimens (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005; Shepherd, Ginsberg, Patterson, et al., 1989; Hara, Ohta, Ichinose, et al., 1991/Hara, Ichinose, Kuda et al., 1991), but not for all included patients.

Study Populations. Inclusion and exclusion criteria (Summary Table 43, Appendix Table 8A)* showed that only the Rostad, Naalsund, Jacobsen, et al. (2004) registry analysis restricted their study population to patients with very early limited stage disease (N0 patients clinically staged Ia or Ib). However, Rostad, Naalsund, Jacobsen, et al. (2004) did not report TRTx or PCI use, and excluded 18 patients who received adjuvant chemotherapy after surgery from their analysis. Thus, none of the eight non-randomized comparisons addressed the population of interest given contemporary treatment with versus without surgery.

Results. Four of eight nonrandomized studies reported significantly longer survival for the group given surgery than for the comparison group managed without surgery (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005; Shepherd, Ginsberg, Patterson, et al., 1989; Friess, McCracken, Troxell, et al., 1985; George, Fitzgerald, Brown, et al., 1986; see Summary Table 8B, Appendix Table 8E). The Badzio case-control study (Badzio, Kurowski, Karnicka-Mlodkowska, et al., 2004/Badzio, Jassem, Kurowski, et al., 2005) also reported a statistically significant increase in time to relapse or progression for those given surgery. No non-randomized comparison evaluated quality of life outcomes.

One cannot exclude the influence of patient selection and other biases in the survival results from non-randomized studies. Most did not report adequate details to evaluate the similarity of study groups with respect to baseline characteristics and prognostic factors (Table 44, Appendix Tables 8b and 8H). Information also was inadequate to determine whether patients in each group were managed similarly with respect to chemotherapy and radiation therapy regimens (Table 44, Appendix Table 8C).

Adverse Events

Perioperative mortality was 2.9 percent in the Lad, Piantadosi, Thomas, et al. (1994) RCT (Table 47, Appendix Table 8G).* It was zero in the Liao, Zhao, Zhou, et al. (1995) RCT and in three reporting non-randomized comparisons. Only two of these five studies reported treatment-related mortality in the comparison groups managed without surgery (Liao, Zhao, Zhou, et al., 1995; George, Fitzgerald, Brown, et al., 1986). Only the Shepherd, Ginsberg, Patterson, et al. (1989) study reported other adverse events, but did not report their rates in the comparison group.

Conclusions

For this question, we sought randomized and nonrandomized studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials and 8 nonrandomized comparative studies were included in the review, but none provided evidence that directly address the question.

None of these comparisons studied a homogeneous group of patients with respect to nodal status; nor were separate outcomes reported for the subgroup of patients without nodal involvement. Moreover, the treatment regimens used had limited relevance to contemporary

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

treatment settings; for example, 5 studies did not use platinum based chemotherapy for any patients, and the remaining 3 used platinum based therapy only for some patients. Thus no conclusion can be drawn on the outcomes of management of very early limited SCLC with versus without surgery.

Key Question 9

What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease (relapse or progression within 3 months of primary treatment).

Overview

Two types of studies were sought: randomized, controlled trials (RCTs) that compared alternative chemotherapy regimens for relapsed, progressive, or extensive-stage SCLC; and phase II multicenter, prospective trials reporting on at least 25 patients treated with a single regimen that reported at least one health outcome of interest. Health outcomes included: duration of survival; disease-free survival and/or progression-free survival; quality of life; treatment-related adverse effects; objective tumor response rates; and response durations.

The primary focus here is on RCTs (Summary Tables 48–51; Appendix Tables 9A–9G).* The main purpose of single-arm phase II trials is to assess responsiveness to a chemotherapy regimen and select treatments for further testing in RCTs. Phase II trials in Appendix Tables 9H-9M* are presented mainly to illustrate the regimens that have been tried on relapsed or progressive SCLC. The lack of comparisons between regimens within such trials limits their usefulness to this Review. Several recent studies that reported encouraging response data will be noted.

Randomized, Controlled Trials

Among 9 RCTs meeting selection criteria, sample sizes ranged from 32 to 610 and they collectively included 1,415 patients. As shown in Table 48, each of the 9 trials compared different sets of chemotherapy regimens. Seven trials compared 2 regimens and the Wolff, Birch, Sarma, et al. (1986) trial compared 3. Six studies specifically noted that second-line regimens were compared (von Pawel, Gatzemeier, Pujol, et al., 2001,; von Pawel, Schiller, Shepherd, et al., 1999; Postmus, Smit, Kirkpatrick, et al., 1993; Trillet-Lenoir, Lasset, Arpin, et al., 1992; O'Bryan, Crowley, Kim, et al., 1990; Spiro, Souhami, Geddes, et al. 1989). The study by Sculier, Lafitte, Lecomte, et al. (2002) stated that patients had previously undergone chemotherapy that did not include cisplatin and etoposide, but did not specify the distribution of number of previous regimens. It was also unspecified by O'Brien, Ciuleanu, Tsekov, et al.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

(2005). Wolff, Birch, Sarma, et al. (1986) described this distribution: 80 percent had previously had 1 chemotherapy regimen, 14 percent had 2; and 6 percent had 3.

Data on age, gender and performance status were reported by all studies except von Pawel, Schiller, Shepherd, et al. (1999), which only give performance status. O'Brien, Ciuleanu, Tsekov, et al. (2005) did not provide separate gender distributions for the two groups. The study by Spiro, Souhami, Geddes, et al. (1989) was a 2-stage randomized trial. In the first stage, patients were randomized to either 4 or 8 cycles of primary chemotherapy consisting of cyclophosphamide, vincristine and etoposide. The second stage randomized patients at relapse to either methotrexate plus doxorubicin or supportive care. Two pairs of first stage groups were compared at the second stage and shown to be similar on age, gender, performance status and stage. Where information was available, groups appeared comparable on these characteristics.

Summary Table 48. RCTs Comparing Alternative Chemotherapy Regimens for Relapsed, Progressive, or Extensive-Stage SCLC

	N Grp1	N Grp2	N Grp3	Regimen 1	Regimen 2	Regimen 3	Previous Regimens	pub type	quality rating
O'Brien, Ciuleanu, Tsekov, et al., 2005	70	71		po T	BSC			Abstr	?
Sculier, Lafitte, Lecomte, et al., 2002	31	34		PE	CbPE		No PE; EVI, VAC, RTx, Surgery	Full	Fair
von Pawel, Gatzemeier, Pujol, et al., 2001	52	54		po T	iv T			Full	Fair
von Pawel, Schiller, Shepherd, et al., 1999	107	104		iv T	CAV		Platinum, CAV, PE+CAV, RTx, Immuno-therapy, Surgery	Full	Fair
Postmus, Smit, Kirkpatrick, et al., 1993	43	25		VIMP	CDE			Full	Fair
Trillet-Lenoir, Lasset, Arpin, et al., 1992	15	17		Low PE	High PE			Full	Poor
O'Bryan, Crowley, Kim, et al., 1990	45	58		BTOC	PE		CAV, E, other	Full	Poor
Spiro, Souhami, Geddes, et al., 1989	294	290		MA	BSC		CV	Full	Poor
Wolff, Birch, Sarma, et al., 1986	26	27	26	E100	E200	E300	1-3 CTx regimens, RTx, Surgery	Full	Poor

Abbreviations table provided at the end of the Report.

Summary Table 49. Sample and Treatments: Treatment of Recurrent/Progressive Disease

Study	Inclusion	Chemotherapy Agents	Age (yr)	Gender (%)	Performance Status (%)
O'Brien, Ciuleanu, Tsekov, et al., 2005	relapsed SCLC ineligible for further IV CTx	po T topotecan BSC best supportive care	po T / BSC mn md 60 / 59 rng sd	All M 73 F 27	PS / po T / BSC 0/1 / 73 / 67
Sculier, Lafitte, Lecomte, et al., 2002	proven SCLC prior CTx did not include PE	PE cisplatin etoposide CbPE carboplatin cisplatin etoposide	PE / CbPE mn md 58 / 59 rng 41-73 / 39-70 sd	PE / CbPE M 84 / 76 F 16 / 24	KPS / PE / CbPE 60-70 / 45 / 32 80-100 / 55 / 68
von Pawel, Gatzemeier, Pujol, et al., 2001	limited or extensive SCLC recurrence ≥ 3 mo after CR/PR to 1st-line CTx	po T topotecan iv T topotecan	po T / iv T mn 59.9 / 58.2 md rng 38-79 / 35-74 sd	po T / iv T M 75.0 / 79.6 F 25.0 / 20.4	PS / po T / iv T 0 / 19.2 / 33.3 1 / 65.4 / 38.9 2 / 15.4 / 27.8
von Pawel, Schiller, Shepherd, et al., 1999	progressive, limited or extensive SCLC PD ≥ 60 d after 1st-line CTx	iv T topotecan CAV cytoxan doxorubin vincristine			ECOG / iv T / CAV 0 / 16.8 / 19.2 1 / 59.8 / 61.5 2 / 23.4 / 19.2
Postmus, Smit, Kirkpatrick, et al., 1993	proven SCLC PD ≤ 3 mo of last CTx 1st-line CTx: IMP, VP or CDE; PD after IMP/VP has 2nd-line CDE; PD after CDE had VIMP	VIMP vincristine ifosfamide mesna carboplatin CDE cytoxan doxorubicin etoposide	IMP / VP / CDE mn md 57 / 58 / 55 rng 38-69 / 39-73 / 43-67 sd	MP / VP / CDE M 71 / 86 / 88 F 29 / 14 / 12	ECOG / IMP / VP / CDE 0 / 24 / 18 / 20 1 / 43 / 45 / 40 2 / 24 / 32 / 20 3 / 10 / 5 / 20
Trillet-Lenoir, Lasset, Arpin, et al., 1992	relapsed SCLC after 1st-line CTx	PE1 cisplatin 20 etoposide 60 PE2 cisplatin 40 etoposide 100	PE1 / PE2 mn 56.73 / 52.47 md rng sd 8.7 / 5.95	PE1 / PE2 M 100 / 88 F 0 / 12	KPS / PE1 / PE2 mn / 79.17 / 74.71 sd / 13.82 / 10.06
O'Bryan, Crowley, Kim, et al., 1990	failed or relapsed SCLC after 1st-line CTx	BTOC vincristine thiotepa cytoxan carmustine PE cisplatin etoposide	BTOC / PE mn md 58 / 61 rng 41-75 / 38-76 sd	BTOC / PE M 80 / 64 F 20 / 36	KPS / BTOC / PE 0-1 / 53 / 39 2-3 / 47 / 61

Abbreviations table provided at the end of the Report.

Summary Table 49. Sample and Treatments: Treatment of Recurrent/Progressive Disease (continued)

Study	Inclusion	Chemotherapy Agents	Age (yr)	Gender (%)	Performance Status (%)
Spiro, Souhami, Geddes, et al., 1989	histologically, cytologically proven SCLC; < 75;	MA methotrexate doxorubicin BSC best supportive care			
Wolff, Birch, Sarma, et al., 1986	recurrent SCLC, prior CTx did not include E	E100 etoposide 100 E200 etoposide 200 E300 etoposide 300	100 200 300 < 50 19 11 15 50-60 38 56 46 > 60 42 33 31	100 200 300 M 58 93 81 F 42 7 19	KPS 100 200 300 60 0 15 0 70 46 33 46 80 27 41 31 90 19 7 12 100 8 4 12

Summary Table 50. Efficacy Outcomes: Treatment of Recurrent/Progressive Disease

Study	Overall Survival (%)	N	Med	1 yr	Test	Tumor Response (%)	N	CR	PR	SD	PD	NE	Test	Med Dur (wks)
O'Brien, Ciuleanu, Tsekov, et al., 2005		N	Med	1 yr		po T	71	7		44				
	po T	71	26 wks	49 (6 mo)		BSC	70							
	BSC	70	14 wks	26										
	HR=0.64 (95% CI: 0.45, 0.90, p=0.0104)													
Sculier, Lafitte, Lecomte, et al., 2002	PE	31	18.9 wks	18	Log-rank,	PE	31	0	29					22.6
	CbPE	34	33.0 wks	19	p=0.11	CbPE	34	9	38					33.9
von Pawel, Gatzemeier, Pujol, et al., 2001	po T	52	32.3 wks	~25	adjusted	po T	52	1.9	21.2	19.2	30.8	26.9	Difference in ORR=	18.1
	iv T	54	25.1 wks	~8	RR=0.90 (95% CI 0.55, 1.47)	iv T	54	3.7	11.1	29.6	42.6	13.0	8.3% (95% CI -6.6%, 23.1%, NS)	13.9
von Pawel, Schiller, Shepherd, et al., 1999	iv T	107	25.0 wks	14.2	Log-rank,	iv T	107	0.0	24.3	19.6	45.8	10.3	Difference in ORR,	14.4
	CAV	104	24.7 wks	14.4	p=0.772, Adjusted RR=1.17 (p=0.322)	CAV	104	1.0	17.3	11.5	52.9	17.3	P=0.285	15.3 (p=0.300)
Postmus, Smit, Kirkpatrick, et al., 1993	VIMP	43	19 wks			VIMP	25	4	56	8	24	8		16
	CDE	25	22 wks			CDE	43	14	37	19	23	7		19
Trillet-Lenoir, Lasset, Arpin, et al., 1992	PE1	15	13 wks			PE1	15	6.6	20	13.3	60			
	PE2	17	16.5 wks			PE2	17	11.8	23.5	11.8	52.9			
O'Bryan, Crowley, Kim, et al., 1990	BTOC	45	13 wks		RR 1.3	BTOC	45	0	13					
	PE	58	16 wks		(95%CI 0.9, 2.0)	PE	58	2	10				(p=0.91)	
						BTOCgood	11	27						
	BTOCgood	11	10 wks		RR 3.3	PEgood	16	27						
	PEgood	16	35 wks		(95%CI 0.2, 9.1)	BTOCpoor	34	9						
						PEpoor	68	9						
	BTOCpoor	34	14 wks		RR1.1									
	PEpoor	68	12 wks		(95%CI 0.7, 1.8)									

Summary Table 50. Efficacy Outcomes: Treatment of Recurrent/Progressive Disease (continued)

Study	Overall Survival (%)	N	Med	1 yr	Test	Tumor Response (%)	N	CR	PR	SD	PD	NE	Test	Med Dur (wks)
Spiro, Souhami, Geddes, et al., 1989	MA					MA	170	4	19	45	32	1		
Wolff, Birch, Sarma, et al., 1986	E100 E200 E300	26 27 26	12.6 wks 20.0 wks 22.5 wks	~4 ~12 ~24	Log-rank, Gehan-Wilcoxon (p=NS)	E100 E200 E300	26 27 26		4 7 4					

Summary Table 51. Adverse Events: Treatment of Recurrent/Progressive Disease

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value[18]
Treatment-related mortality	O'Bryan 1990	Drug-related deaths	BTOC	45	4		0.28
			PE	84	1		
Alopecia	Sculier 2002		PE	28		21 (3/4)	0.15
			CbPE	31		39	
	von Pawel 2001		po T	52	1.9	0.0	0.06
			iv T	54	13.0	0.0	
	von Pawel 1999		iv T	107		0.0 (3/4)	1.0
			CAV	104		0.0	
Fatigue	von Pawel 2001		po T	52	5.8	0.0	0.36
			iv T	54	1.9	0.0	
	von Pawel 1999		iv T	107		4.7 (3/4)	0.28
			CAV	104		8.7	
Diarrhea	von Pawel 2001		po T	52	7.7	0.0	0.054
			iv T	54	0.0	0.0	
	von Pawel 1999		iv T	107		0.9 (3/4)	1.0
			CAV	104		0.0	
Nausea	O'Brien 2005		po T	71	1		1.0
			BSC	70	0		
	von Pawel 1999		iv T	107		39.3 (3/4)	0.89
			CAV	104		40.4	
Vomiting	O'Brien 2005		po T	71	3		0.50
			BSC	70	0		
	Sculier 2002	Nausea/vomiting	PE	30		7 (3/4)	0.23
				32		0	
	von Pawel 2001		po T	52	11.5	0.0	0.16
			iv T	54	3.7	0.0	
	von Pawel 1999		iv T	107		2.9 (3/4)	1.0
			CAV	104		1.9	
	Wolf 1986	Nausea/vomiting/bloody diarrhea/ stomatitis	E100	26	5	0	0.44
			E200	27	4	0	
			E300	26	10	0	
Anorexia	von Pawel 1999		iv T	107		0.9 (3/4)	1.0
			CAV	104		0.0	
Diarrhea	O'Brien 2005		po T	71	6		0.12
			BSC	70	0		
Lethargy	O'Brien 2005	Fatigue	po T	71	4		1.0
			BSC	70	4		
Neurosensory	O'Brien 2005	Pain	po T	71	3		0.44
			BSC	70	6		
Neuromotor							
Hearing loss							
Esophagitis							

[18] Comparison of grade 3 and above versus others Fisher's exact test.

Summary Table 51. Adverse Events: Treatment of Recurrent/Progressive Disease (continued)

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value[19]
Bronchopulmonary	O'Brien 2005	Dyspnea	po T	71	3		0.32
			BSC	70	9		
	von Pawel 2001	Dyspnea	po T	52	9.6	0	1.0
			iv T	54	9.3	0 (5:1.9)	
			po T	52	1.9	0 (5: 3.8)	0.36
		Pulmonary embolism	iv T	54	0	0 (5: 1.9)	
Pneumonitis	von Pawel 2001	Pneumonia	po T	52	5.8	1.9	0.054
			iv T	54	0.0	0.0	
Hepatic							
Kidney							
Hemorrhage							
Anemia	O'Brien 2005		po T	71	25 (3/4)		
	von Pawel 2001		po T	52	27.5	3.9	1.0
			iv T	54	26.4	3.8	
	von Pawel 1999		iv T	104	39.4	2.9	0.001
			CAV	101	17.8	2.0	
Thrombocytopenia	O'Brien 2005		po T	71		7	
	Sculier 2002		PE	30	17 (3/4)		0.07
			CbPE	32	38		
	von Pawel 2001		po T	52	25.5	27.5	0.85
			iv T	54	24.5	24.5	
	von Pawel 1999		iv T	104	28.8	28.8	<0.001
			CAV	101	9.9	5.0	
	Postmus 1993		VIMP	25	8	45	<0.001
			CDE	43	6	3	
	Trillet-Lenoir 1992		PE1	15	0	7	0.041
			PE2	17	18	24	
	Wolff 1986	Neutropenia	E100	26	0	15	<0.001
			E200	27	0	13	
			E300	26	24	33	
Leukopenia or neutropenia	O'Brien 2005	Neutropenia	po T	71		33	
	Sculier 2002	Leukopenia	PE	30	60 (3/4)		0.76
			CbPE	32	56		
	von Pawel 2001	Leukopenia	po T	52	27.5	17.6	0.006
			iv T	54	45.3	28.3	
		Neutropenia	po T	52	21.6	35.3	<0.001
			iv T	54	25.9	67.3	

[19] Comparison of grade 3 and above versus others Fisher's exact test.

Summary Table 51. Adverse Events: Treatment of Recurrent/Progressive Disease (continued)

Toxicity Type	Study	Description	Group	n	Gr 3 %	Gr 4 %	p value
Leukopenia or neutropenia	von Pawel 1999	Leukopenia	iv T	104	54.8	31.7	0.34
			CAV	101	37.6	43.6	
		Neutropenia	iv T	104	18.3	70.2	0.83
			CAV	99	15.2	71.7	
	Postmus 1993	Leukopenia	VIMP	25	26	40	1.0
			CDE	43	38	25	
	Trillet-Lenoir 1992	Leukopenia	PE1	15	33	13	0.021
			PE2	17	12	76	
	Wolff 1986		E100	26	5	0	<0.001
			E200	27	25	54	
			E300	26	0	86	
Infection	O'Brien 2005	Febrile neutropenia	po T	71		3	
		Neutropenic infections	po T	71		1	
		Sepsis	po T	71		4	
	Sculier 2002		PE	30	3 (3/4)		0.96
			CbPE	33	3		
	von Pawel 2001	Fever	po T	52	3.8	1.9 (5:1.9)	0.20
			iv T	54	1.9	0.0	
Other							

Study Quality. Of the nine RCTs meeting selection criteria, four were rated as being of fair quality (Sculier, Lafitte, Lecomte, et al., 2002; von Pawel, Gatzemeier, Pujol, et al., 2001; von Pawel, Schiller, Shepherd, et al., 1999; Postmus, Smit, Kirkpatrick, et al., 1993, 4 were rated as poor (Trillet-Lenoir, Lasset, Arpin, et al., 1992; O'Bryan, Crowley, Kim, et al., 1990; Spiro, Souhami, Geddes et al. 1989; Wolff, Birch, Sarma, et al. 1986), and one could not be rated because it has only been reported as a conference abstract (O'Brien, Ciuleanu, Tsekov, et al., 2005). The fair trials had moderate flaws mainly in the initial assembly of comparable groups: either the randomization method was inadequately described or insufficient information was available about group baseline characteristics. The 4 poor trials had multiple problems, but 3 failed to define interventions clearly enough. Specifically, the number of intended cycles of chemotherapy was unspecified in these articles.

Overview of Outcomes

Overall Survival. Eight of nine trials reported data on overall survival, but only the study by O'Brien, Ciuleanu, Tsekov, et al. (2005) found a statistically significant difference between groups, in this case favoring oral topotecan over best supportive care.

Time to Progression. Neither of the two studies reporting on time to progression (von Pawel, Gatzemeier, Pujol, et al., 2001; von Pawel, Schiller, Shepherd, et al., 1999) found statistically significant differences between groups.

Quality of Life. The two studies by von Pawel et al. both reported data from a symptom scale that includes 9 domains. Only the earlier study, comparing intravenous topotecan and CAV, mentioned statistically significant differences between treatment groups.

Adverse Events. Specific risks of adverse events varied as expected given that these studies used a variety of treatments. Higher risks of grade 3 and 4 toxicity may be acceptable if a treatment yields a substantial survival advantage. O'Brien, Ciuleanu, Tsekov, et al. (2005) found significantly greater survival for oral topotecan over best supportive care, while toxicities were low. The 2001 trial by von Pawel, Gatzemeier, Pujol, et al. found no difference in survival between oral and intravenous topotecan, but the intravenous route was associated with higher rates of leukopenia and neutropenia. The 1999 study by von Pawel, Schiller, Shepherd, et al. reported no survival difference between intravenous topotecan and CAV, but the topotecan group had higher risks of anemia and thrombocytopenia. Trillet-Lenoir, Lasset, Arpin, et al. (1992) observed similar survival for low and high dose PE, but the high dose group experienced more leukopenia. The small study conducted by Wolf did not find significant differences in survival for 3 doses of etoposide, but there was a trend toward better survival with higher dose, as well as more thrombocytopenia and neutropenia.

Tumor Response. Excluding the O'Brien, Ciuleanu, Tsekov, et al. (2005) and Spiro, Souhami, Geddes, et al. (1989) studies that did not actively treat the control group, none of the other 7 studies found significant differences in tumor response or duration between treatment groups.

O'Brien, Ciuleanu, Tsekov, et al. (2005). Oral Topotecan (po T) vs. Best Supportive Care (BSC).

Study Quality. Since there is insufficient information about this study's methods, study quality could not be rated.

Overall Survival. This study, available only as a conference abstract, randomized 71 patients to oral topotecan and 70 patients to best supportive care. There was a 36 percent reduction in the risk of death for those receiving topotecan (hazard ratio=0.64, 95 percent CI: 0.45–0.90, p=0.0104). Median survival was longer for the topotecan patients (26 weeks vs. 14 wks) and 6-month survival was increased (49 percent vs. 26 percent).

Time to Progression. No data.

Quality of Life. This study administered the EQ-5D health-related quality of life questionnaire and found a significantly faster rate of deterioration in the BSC group.

Adverse Events. No significant differences were found in the incidence of these adverse events: vomiting, diarrhea, fatigue, pain and dyspnea. No hematologic toxicity was noted in the abstract for the BSC group, but in the topotecan group 7 percent had grade 3 or 4 anemia, 7 percent had grade 4 thrombocytopenia and 33 percent had grade 4 neutropenia. In the topotecan group, the risk of febrile neutropenia was 3 percent, while 1 percent had neutropenic infections and 4 percent developed sepsis.

Tumor Response. The abstract noted that the response rate for topotecan was 7 percent, but it was unclear what proportions had complete or partial responses. A further 44 percent experienced a stable disease after topotecan.

Summary. Compared with best supportive care, oral topotecan significantly improves survival in patients with relapsed SCLC. The decline in quality of life is faster in patients receiving best supportive care. Neutropenia is the most common major adverse event. Careful assessment of the methodologic quality of this study awaits full publication beyond a conference abstract.

Sculier, Lafitte, Lecomte, et al. (2002). Cisplatin/Etoposide (PE) vs. Carboplatin/Cisplatin/Etoposide (CbPE).

Study Quality. This study was rated as fair, its main shortcoming concerned its lack of detail about the randomization method and lack of blinded interpretation of tumor response, which was the primary outcome.

Overall Survival. This trial reported on 31 patients who received cisplatin and etoposide and 34 patients who received that regimen plus carboplatin. These investigators found a median survival advantage of 14.1 weeks for the CbPE group relative to the PE group, although the difference was not statistically significant (p=0.11).

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. Although nearly twice as CbPE patients as PE patients had grade 3 or 4 alopecia (39 percent vs. 20 percent), the difference was not statistically significant. The authors reported that 19 percent of patients receiving PE experienced grade 3 or 4 thrombocytopenia, compared with 12 percent receiving CbPE, a nonsignificant difference. Grade 3 or 4 leukopenia occurred in 60 percent given PE and 56 percent given CbPE (p=0.97). The same percentage of patients (3 percent) in both groups developed infections.

Tumor Response. Thie trial found an ORR of 47 percent for CbPE and an ORR of 29 percent for PE. Median response duration was 33.9 weeks for CbPE and 22.6 weeks for PE. No statistical test results for these outcomes were provided.

Summary. The data from this trial suggested slightly improved survival and tumor response in adding carboplatin to the combination of cisplatin and etoposide. This small underpowered study did not find significant differences between groups on any outcome. It is important to remember that this trial enrolled only patients who did not have previous therapy with platinum and etoposide.

von Pawel, Gatzemeier, Pujol, et al. (2001). Oral Topotecan (po T) vs. Intravenous Topotecan (iv T).

Study Quality. This trial was rated as fair; the principal problem was lack of detail about the randomization method.

Overall Survival. These authors randomized 52 patients to oral topotecan and 54 patients to intravenous topotecan. They reported that median survival using oral topotecan was 32.3 weeks, compared with 25.1 weeks for intravenous topotecan. The difference was not statistically significant.

Time to Progression. These authors found that median time to disease progression was similar in the oral (14.9 weeks) and intravenous (13.1 weeks) topotecan groups. The difference was not statistically significant.

Quality of Life. This article stated that both oral and intravenous topotecan were associated with symptom improvement, but specific results of statistical tests were not given.

Adverse Events. Significant differences were not observed between groups on the following grade 3 and grade 4 outcomes: alopecia, vomiting, dyspnea, pulmonary embolism, pneumonia, anemia, thrombocytopenia and fever. Grade 3 diarrhea was significantly more common in the group receiving oral topotecan (7.7 percent vs. 0 percent). Grade 3 leukopenia was significantly more frequent in the intravenous group (45.3 percent vs. 27.5 percent). Grade 4 neutropenia occurred significantly more often among intravenous topotecan patients (67.3 percent vs. 35.3 percent).

Tumor Response. The ORR for oral topotecan was 23.1 percent and the proportion for intravenous topotecan was 14.8 percent. The difference was not statistically significant.

Summary. This study observed no significant difference in survival between those give oral or intravenous topotecan. The difference in overall response was not significant, but favored the oral route. Some hematologic toxicities were more common for intravenous, but most other adverse events occurred at similar rates.

von Pawel, Schiller, Shepherd, et al. (1999). Intravenous Topotecan (iv T) vs. Cyclophosphamide/Doxorubin/Vincristine (CAV).

Study Quality. This study was rated as fair. While the randomization method was sufficiently described and seemed adequate, age and gender distributions were not specified, co it could not be established if groups were comparable on these characteristics at baseline.

Overall Survival. The total assigned to intravenous topotecan was 107, while 104 received CAV. Median survival was nearly identical for intravenous topotecan (25 weeks) and CAV (24.7 weeks). The analysis that adjusted for covariates was not statistically significant.

Time to Progression. Median progression-free survival differed by only 1 week between the iv T and CAV groups in this trial.

Quality of Life. The percentage of patients improved on symptoms was greater for intravenous topotecan than CAV for all domains except hemoptysis, which showed a nonsignificant difference of 6.6 percent. Five domains significantly favored intravenous topotecan: dyspnea, anorexia, hoarseness, fatigue and impaired activities of daily living.

Adverse Events. Significant differences were not found between groups for these grade 3 or 4 outcomes: fatigue, nausea, vomiting and anorexia. The group receiving intravenous topotecan had a risk of grade 3 or 4 anemia that was twice that of the CAV group: 42.3 percent versus 19.8 percent ($p<0.001$). The rates of both grade 3 and grade 4 thrombocytopenia were significantly higher for the intravenous topotecan group, compared with the CAV group (grade 3: 28.8 percent vs. 9.9 percent; grade 4: 28.89 percent vs. 5 percent). Risks of grade 3 or 4 leukopenia were similar for intravenous topotecan (76.5 percent) and CAV (81.2 percent), as were grade 3 or 4 neutropenia (78.5 percent) and CAV (76.9 percent).

Tumor Response. Intravenous topotecan had an ORR of 24.3 percent, while CAV had an ORR of 18.3 percent, a difference that was not statistically significant.

Summary. Intravenous topotecan and CAV produced similar overall and progression-free survival. Five symptom domains showed significantly greater improvement in the intravenous topotecan group. Anemia and thrombocytopenia was more common among those receiving intravenous topotecan.

Postmus, Smit, Kirkpatrick, et al. (1993). Vincristine/Ifosfamide/Mesna/Carboplatin (VIMP) vs. Cyclophosphamide/Doxorubicin/Etoposide (CDE).

Study Quality. This study was rated as fair, due to missing information about the method of randomization.

Overall Survival. This study did not include the results of a statistical test on survival duration, but median survival differed between groups by only 3 weeks and given the small sample (n=68; 43 had VIMP and 25 had CDE), this is probably not statistically significant.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. In this study, there was a significantly higher incidence of grade 3 or 4 thrombocytopenia in the VIMP group (53 percent) compared with the CDE group (9 percent). Incidence of grade 3 or 4 leukopenia was similar for VIMP (66 percent) and CDE (63 percent).

Tumor Response. This study did not mention statistical test results. The ORR for the VIMP group was 60 percent and the figure for the CDE group was 51 percent.

Summary. The VIMP and CDE groups did not differ significantly on survival or tumor response. The only outcome that differed was the incidence of grade 3 or 4 thrombocytopenia, which was significantly more frequent in the VIMP group.

Trillet-Lenoir, Lasset, Arpin, et al. (1992). Cisplatin 20/Etoposide 60 (PE1) vs. Cisplatin 40/Etoposide 100 (PE2).

Study Quality. This study was rated as poor because the randomization method was not sufficiently described, no primary outcome was identified, interventions were incompletely described and it was unclear if outcome measurement was valid, reliable and equal.

Overall Survival. This study found that the high-dose PE2 group (n=15) had a longer median survival than the low-dose group (n=17) by 3.5 weeks. There was no mention of statistical test results on survival, but this trial was very small and the difference is unlikely to be statistically significant.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. This study showed that high-dose PE was associated with a significantly higher risk of grade 3 or 4 thrombocytopenia than low-dose PE (42 percent vs. 7 percent). Grade 4 leukopenia was much more frequent (76 percent vs. 13 percent) in the high-dose PE group.

Tumor Response. The high-dose PE group had an ORR of 26.6 percent while the low-dose group achieved an ORR of 35.3 percent. No statistical test findings were noted by the authors, but the small sample size of 32 patients would require a large difference to achieve statistical significance.

Summary. Survival and tumor response were roughly similar in the low-dose and high-dose PE groups, while there were higher rates of thrombocytopenia and leukopenia in the high-dose group.

O'Bryan, Crowley, Kim, et al. (1990).
Vincristine/Thiotepa/Cyclophosphamide/Carmustine (BTOC) vs. Cisplatin/Etoposide (PE).

Study Quality. This study's quality was rated as poor owing to lack of information about the randomization technique, lack of blinding for the primary outcome (tumor response), and lack of details about treatment.

Overall Survival. There were 45 patients in the BTOC group and 58 in the PE group. The authors presented 3 sets of results: all patients; good prognosis patients; and poor prognosis patients. None of the analyses demonstrated a statistically significant difference between BTOC and PE. Median survival nonsignificantly favored PE among all patients and good prognosis patients. The difference was large for good prognosis patients (25 weeks), but only 27 patients were in this subset. The relation between treatments was reversed for bad prognosis patients: median survival was better by 2 weeks for BTOC over PE.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. The trial reported that 4 percent of patients in the BTOC group experienced drug-related death, compared with 1 percent for PE, a difference that was not statistically significant.

Tumor Response. The trial found no statistically significant difference between the ORR for BTOC (13 percent) and PE (12 percent). Identical ORRs were obtained for treatment groups with both good and poor prognoses.

Summary. This trial found no significant differences between BTOC and PE in survival, tumor response or drug-related death.

Spiro, Souhami, Geddes, et al. (1989). Methotrexate/Doxorubicin vs. Supportive Care

Study Quality. Quality was rated as poor due to lack of details about the randomization technique and a high loss of patients in the second stage of the study (42 percent).

Overall Survival. This outcome was not reported on the basis of the second randomization (to second-line chemotherapy or supportive care), rather it was based on the first randomization to either 4 or 8 cycles of primary chemotherapy. Therefore, it is unclear how patients given chemotherapy or supportive care upon relapse compare in terms of survival.

Time to Progression. As above, this outcome was not presented based on treatment approach given at relapse.

Quality of Life. This outcome was not reported.

Adverse Events. Toxicity data were not provided for second-line chemotherapy.

Tumor Response. Of the 294 patients randomized to receive chemotherapy at relapse, 170 received it and were assessed for response. Complete response was achieved in 4 percent and partial response was observed in 19 percent.

Summary. Results were presented from this study mainly based on randomization for first-line chemotherapy. An overall response rate of 23 percent to second-line chemotherapy was observed, but other data are lacking on outcomes after randomization at relapse, comparing chemotherapy and supportive care.

Wolff, Birch, Sarma, et al. (1986). Etoposide 100 (E100) vs. Etoposide 200 (E200) vs. Etoposide 300 (E300).

Study Quality. The Wolff, Birch, Sarma, et al. (1986) trial received a poor quality rating due to uncertainty on the comparability of groups at baseline, lack of blinded assessment of tumor response, the primary outcome, lack of detail about treatments and inappropriate analysis of results.

Overall Survival. There were 26, 27 and 26 patients in the groups receiving 100 mg, 200 mg and 300 mg of etoposide, respectively. No statistically significant differences were found between etoposide dose groups. The 200 mg and 300 mg groups were similar in median survival (20 weeks and 22.5 weeks, respectively), while the median for 100 mg group was 12.6 weeks.

Time to Progression. No data.

Quality of Life. No data.

Adverse Events. There was a significant dose gradient for higher grade thrombocytopenia in 3 groups given single agent etoposide therapy: 5 percent for 100 mg; 79 percent for 200 mg; and 86 percent for 300 mg. The trial found that grade 3 or 4 neutropenia was much more likely in the etoposide 300 mg group (57 percent), compared with those receiving 100 mg (15 percent) or 200 mg (13 percent).

Tumor Response. Only PRs were achieved in each of the 3 etoposide groups: 4 percent for 100 mg; 7 percent for 200 mg; and 4 percent for 300 mg.

Summary. Significant differences in survival and tumor response were not observed between 3 different doses of single-agent etoposide. Thrombocytopenia and leukopenia were more common for higher dose etoposide

Phase II Trial Evidence

Among multicenter phase II trials published since 2000 (Summary Table 52; see Appendix Tables 9H–9M),[20] 5 deserve brief mention due to encouraging response data. While overall response rates of 20 percent or higher were reported by these trials, high rates of hematologic

[20] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/lungcansmall/lungcan.pdf.

toxicity were observed. Each used a different treatment regimen. The largest study was Ardizzoni, Manegold, Debruyne, et al. (2003, n=116); all others enrolled fewer than 50 patients.

Ando, Kobayashi, Yoshimura, et al. (2004) reported data for 25 patients who were given irinotecan plus cisplatin for refractory or relapsed SCLC after first-line etoposide therapy. Partial responses were observed in 81 percent of 16 relapsed patients and 78 percent of 9 refractory patients. Grade 3 thrombocytopenia was seen in 12 percent and 24 percent had grade 3 or 4 neutropenia.

Summary Table 52. Multicenter Phase II Trials of Note for Key Question 9

Study	Patient Selection	N	Regimen	Previous Treatment (%)
Ando, Kobayashi, Yoshimura, et al., 2004	refractory (off CTx < 2 mo) or relapsed (off CTx > 2 mo) after initial etoposide regimen	25	irinotecan+cisplatin	PE 16 CbP 84 TRTx 20 Surgery 4
Ardizzoni, Manegold, Debruyne, et al., 2003	relapsed after 1st-line CTX (except camptothecin analogues; cisplatin allowable if responsive, CTx ≥ 6 mo before	116	topotecan+cisplatin	Sen Ref TRTx 69 31 med # CTX 3 3 Cisplatin 22 5 Carbopl 24 36 Etopos 90 83
Kosmas, Tsavaris , Malamos, et al. et al. ,2001	relapsed after CbE CTx ± TRTx; not curable by other 2nd-line CTx or RTx	33	paclitaxel+ifosfamide+cisplatin	CTx 100 TRTx 42
Kakolyris, Mavroudis, Tsavaris, et al., 2001	refractory; had failed 1 prior 1st-line CTx	32	paclitaxel+carboplatin	EP 84 CAB 16 RTx 47 Surgery 6
Sonpavde, Ansari, Walker, et al., 2000	recurrent; 1 prior combination CTx regimen	46	doxorubicin+paclitaxel	Platinum-E ± VIP 100 RTx 59

Ardizzoni, Manegold, Debruyne, et al. (2003) collected outcomes for 110 patients who received topotecan plus cisplatin for either sensitive (n=68) or refractory (n=42) SCLC. Among sensitive patients, a CR was seen in 1.5 percent and PR in 27.9 percent. The incidence of grade 3 or 4 leukopenia was 80.9 percent and neutropenia occurred in 76.5 percent. At least 1 episode of febrile neutropenia happened in 19 percent. There was a PR rate of 23.8 percent in refractory patients. Grade 3 or 4 leukopenia was observed in 75.6 percent and the risk of neutropenia was the same. At least 1 instance of febrile neutropenia occurred in 15 percent.

Kosmas, Tsavaris, Malamos, et al. (2001) enrolled 33 patients who relapsed after initial treatment with carboplatin plus etoposide. Second-line therapy was paclitaxel, ifosfamide and cisplatin. The CR rate was 24.2 percent and the PR rate was 48.5 percent. Grade 3 anemia was seen in 18 percent. Grade 3 thrombocytopenia affected 36 percent. Grade 3 or 4 leukopenia occurred in 73 percent, the rate of neutropenia was 91 percent. Grade 3 febrile neutropenia was found in 18 percent.

Kakolyris, Mavroudis, Tsavaris, et al. (2001) gave data for 29 patients who were refractory after first-line chemotherapy and then were offered paclitaxel plus carboplatin. CR was achieved in 3 percent and PR in 22 percent. Grade 3 or 4 neutropenia was observed in 48 percent.

Sonpavde, Ansari, Walker, et al. (2000) recruited 46 patients who recurred after first-line therapy and were given doxorubicin plus carboplatin. CRs were measured in 7 percent and PRs in 35 percent. Grade 3 or 4 granulocytopenia occurred in 80 percent.

Conclusions

Nine randomized trials have made 9 different comparisons for second- or subsequent-line treatment of SCLC. Two randomized trials have directly compared chemotherapy with best supportive care for recurrent SCLC. The first studied second-line methotrexate plus doxorubicin and found an overall response rate of 23 percent for the chemotherapy arm. The second reported that oral topotecan resulted in a modest but significant improvement in survival, slower decline in quality of life and high grade neutropenia in one third. In another trial, oral topotecan had nonsignificantly higher median survival and overall response rate than intravenous topotecan, which had higher risks of leukopenia and neutropenia. A study that addressed the addition of carboplatin to cisplatin and etoposide is of limited use given that it in enrolled only those who did not receive first-line cisplatin and etoposide, which is the current standard regimen. One small study comparing 3 doses of monotherapy etoposide did not find significant survival differences, but a trend favored the highest dose, along with increased thrombocytopenia and neutropenia. Other studies found higher rates of adverse events for one treatment over another, but no associated survival advantage that would offset increased high grade toxicity. One example is a comparison of oral and intravenous topotecan which reported that the intravenous route was associated with higher rates of leukopenia and neutropenia. A study comparing intravenous topotecan and CAV showed that the topotecan group had higher risks of anemia and thrombocytopenia. High dose PE had more leukopenia than low dose PE.

Five multicenter phase II trials of note published since 2000 have reported overall response rates of 20 percent or more. Only one study, using topotecan plus cisplatin, enrolled more than 50 patients. Approximately one-fourth of both sensitive and refractory patients responded. Three-quarters or more of both patient groups had high grade leukopenia and neutropenia. A small study of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide and cisplatin achieved a high ORR and high grade leukopenia in nearly all patients. One quarter of those given paclitaxel plus carboplatin had a response and about half had high grade neutropenia. In a study of doxorubicin plus carboplatin, nearly half responded, but 4 out of 5 had grade 3 or 4 granulocytopenia. Whether these regimens should be used in practice awaits randomized trials.

Chapter 4. Conclusions

1. For limited-stage SCLC, what are the relative benefits and harms of TRTx combined with chemotherapy either in alternating fashion, concurrently, or sequentially?

One multicenter trial and one single-center trial (n=307) compared concurrent and sequential TRTx. Results are not conclusive but suggest better outcomes for concurrent TRTx. Overall survival adjusted for confounders significantly favored concurrent TRTx in the Takada, Fukuoka, Kawahara, et al. trial (2002; n=228), although unadjusted results were not significant. Additionally, the Park, Kim, Jeong, et al. (1996) trial found significantly longer response duration for concurrent TRTx. Of 11 types of adverse events reported, only leukopenia occurred significantly more frequently in the concurrent TRTx group in both studies.

No conclusions could be drawn on the relative benefits and harms of TRTx combined with chemotherapy in alternating fashion. No significant differences in survival or progression-free survival were found in any of four trials. Two trials (n=458) compared alternating to sequential TRTx; one trial (n=156) compared alternating to concurrent TRTx; and one trial (n=199) compared early alternating and late alternating TRTx.

2. For limited-stage SCLC, do outcomes differ if concurrent TRTx is given in early versus late chemotherapy cycles?

Overall, the evidence is equivocal, either finding no difference or a small advantage for early TRTx. One multi-center trial of good quality significantly favored concurrent therapy given in an early cycle (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988), as did 2 smaller trials. Of the two larger multi-center trials that that found no significant difference in survival, one did not use platinum chemotherapy (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988) and the other has not been published in full-text (James, Spiro, O'Donnell, et al., 2003).

Leukopenia/neutropenia appeared to be more common with early concurrent TRTx, although differences were statistically significant in only two of six reporting trials. Other events do not appear to be more frequent with either early or late TRTx. However, evidence is limited as adverse events were not reported consistently across all trials

Meta-analysis was performed on survival outcome of early versus late TRTx in an attempt to obtain clearer results. For purposes of the meta-analysis, the studies selected for Key Questions 1 and 2 were viewed as comparing early and late TRTx. Therefore, these studies were pooled to give a more robust analysis of early versus late TRTx. Overall, we did not find significant reductions in 2- and 3-year mortality for early TRTx over late TRTx. The RR at 2 years was 0.921 (95 percent CI: 0.844–1.005) and the RR at 3 years was 0.991 (0.955–1.029). Although the overall analysis was not significant, sensitivity analysis suggests that if there is an advantage

favoring early TRTx it would accompany use of hyperfractionation and possibly use of platinum chemotherapy.

3. For limited-stage SCLC, do outcomes (survival, toxicity, quality of life) of primary therapy differ if one varies dose rate, treatment interval, or fractionation scheme for delivering radiotherapy? Comparisons of interest include:

- **accelerated regimens (>10 Gy per week completed over a short interval) versus standard duration regimens (≤10 Gy per week) versus split courses delivered over the standard interval; and**

- **single daily fractions versus hyperfractionated (two or more daily fractions or concomitant boost).**

Evidence to compare dose rates, treatment intervals, or fractionation schemes is limited. Two RCTs compared one versus two fractions a day for previously untreated SCLC. One compared an accelerated regimen versus the standard duration, while the other compared a split-course regimen versus the standard duration.

Compared to a single daily fraction, two daily fractions delivered concurrently with platinum chemotherapy improved overall survival in a large multicenter trial of good quality (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000; N=417). More specifically, this trial showed that starting TRTx with the first cycle of cisplatin-etoposide chemotherapy and giving it in two daily fractions over 3 weeks increased overall survival (23 vs. 19 months, log rank p=0.04) when compared with the same dose begun at the same time but given in one daily fraction over 5 weeks.

Evidence from the second trial is difficult to interpret, since multiple variables were studied simultaneously (Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999; N=161). However, it found no difference in overall survival between treatment arms managed with one versus two fractions per day.

Neither trial reported data on quality of life. Esophagitis was the only adverse event reported more frequently with two fractions per day than with one fraction per day in both trials.

4. What are the relative benefits and harms (survival, toxicity, and quality of life) of adding thoracic radiation therapy to chemotherapy for primary treatment of extensive-stage SCLC?

Evidence from one single-center RCT (Jeremic, Shibamoto, Nikolic, et al., 1999; N= 99) suggests that adding concurrent TRTx improves survival of patients with extensive-stage disease

that responds to an initial three cycles of platinum/etoposide chemotherapy with a complete response outside the thorax and at least a partial response in the thorax. Uncontrolled data from the same trial suggest little to no benefit for patients who achieve no better than a partial response outside the thorax. With the regimens used in this trial, concurrent TRTx apparently increases grades 3 and 4 esophagitis.

No other trials have reproduced the results reported by Jeremic, Shibamoto, Nikolic, et al. (1999). Four earlier trials (N=129) are limited by small sample sizes and non- platinum chemotherapy regimens; none used concurrent TRTx.

5. What are the benefits and harms (survival, toxicity and quality of life) of prophylactic cranial irradiation?

Evidence from an individual patient data Cochrane review and meta-analysis on seven RCTs (N=987) conducted by the PCI Overview Collaborative Group shows that PCI modestly improves survival of SCLC patients in CR after primary therapy. PCI increases the proportion alive at 3 years from 15.3 percent to 20.7 percent (P=0.01), an absolute increase of 5.4 percent. PCI also significantly decreases the risk for brain metastasis and increases the likelihood of disease-free survival. The sole trial reported after the meta-analysis confirms effects of PCI on brain metastasis, and generally agrees with the modest effect on overall survival.

Subgroup analyses using individual patient data showed that PCI significantly decreases brain metastases for SCLC patients in CR regardless of age, disease stage or performance status at diagnosis, and whether or not TRTx is part of the induction regimen. Although PCI does not have significant effect on survival for most of these subgroups, it does not appear that any of these subgroups benefits more or less than others.

Additional subgroup analyses suggested that increasing the PCI dose from 8 to 40 Gy and starting PCI within the first 6 months after achieving CR may decrease the likelihood of brain metastasis. Patient gender also may interact with effects of PCI on survival. However, these hypotheses, derived from subgroup analyses, require formal testing in RCTs.

Data on acute toxicities of PCI are scant, but those available suggest they are tolerable at the doses used in these trials (8–40 Gy in 1.8 to 3 Gy fractions). Evidence from two trials suggests neuropsychological and cognitive deficits and structural abnormalities on brain CT scans are relatively common among SCLC patients in CR after primary therapy but before PCI. Available evidence on patients who survived 1–2 years, while limited, did not show greater deterioration of existing deficits or more frequent appearance of new abnormalities with PCI than among controls.

6. Does the addition of PET scanning improve the accuracy of staging for patients with SCLC over the use of other techniques, including CT and MRI, without PET?

It is not possible from the limited and poor quality evidence that is available to determine whether the use of PET adds value relative to conventional staging tests for SCLC.

Six studies reporting on a total of 277 patients (range 20–120) provided data on the diagnostic accuracy of PET in SCLC. The evidence suggests that, except for detection of brain metastases, PET added to conventional staging is more sensitive in detecting disease than conventional staging alone. Upstaging was reported in 4–20 percent of patients and downstaging in 4–13 percent of patients. Three studies reported very high occurrence of patient management changes that were attributed to PET (29–58 percent).

However, the quality of these studies is consistently poor and insufficient detail in reporting was the norm. There is such a high degree of uncertainty about the execution and interpretation of the reference standard in all of these studies that confidence is quite low in estimates of diagnostic and staging accuracy. Although these studies report that PET has correctly upstaged or downstaged the extent of disease, the frequency of incorrect changes in stage attributable to PET is unknown due to incomplete reporting. It is not possible to determine the frequency with which management changes based on PET results were actually beneficial or harmful.

7. What are the outcomes (survival, toxicity and quality of life) of treatments used to manage patients with mixed small cell/non-small cell lung cancers?

No studies meet selection criteria for this question. Very few references from the literature search represented studies of any kind that included patients with mixed histology. No conclusions can be drawn on outcomes of treatment for patients with mixed small cell/non-small cell lung cancers.

8. What is the role of surgery and what is its impact on survival in patients with early stage SCLC? How do available studies define early stage SCLC?

For this question, we sought randomized and nonrandomized studies that compared surgery to no surgery in patients with very early limited SCLC, defined as no preoperative evidence of involved nodes (clinically N0). Two randomized controlled trials and 8 nonrandomized comparative studies were included in the review, but none provided evidence that directly addresses the question.

None of these comparisons studied a homogeneous group of patients with respect to nodal status; nor were separate outcomes reported for a subgroup of patients without evidence of nodal involvement by current staging methods. Moreover, the treatment regimens used had limited relevance to contemporary treatment settings; for example, 5 studies did not use platinum-based chemotherapy for any patients, and the remaining 3 used platinum based therapy only for some patients. Thus no conclusion can be drawn on the outcomes of management of very early limited SCLC with versus without surgery.

9. What are the outcomes of second- or subsequent-line therapy in patients with relapsed or progressive SCLC? Where available data permit, patients with limited- and extensive-stage disease will be addressed separately, as will those with refractory disease.

Nine RCTs address second- or subsequent-line treatment of SCLC, each of which compared different sets of chemotherapy regimens. Two randomized trials directly compared chemotherapy with best supportive care for recurrent SCLC. The first studied second-line methotrexate plus doxorubicin and found an overall response rate of 23 percent for the chemotherapy arm. The second reported that oral topotecan resulted in a statistically significant increase in survival (26 weeks vs. 14 weeks) and slower decline in quality of life. High grade neutropenia occurred in one third of patients. Another trial compared oral versus intravenous topotecan; leukopenia and neutropenia were more frequent with the intravenous route, but survival and response were no greater.

A study that addressed the addition of carboplatin to cisplatin and etoposide is of limited use given that it enrolled only those who did not receive first-line cisplatin and etoposide, which is the current standard regimen. One small study comparing 3 doses of monotherapy etoposide did not find significant survival differences, but a trend favored the highest dose, along with increased thrombocytopenia and neutropenia. Other studies found higher rates of adverse events for one treatment over another, but no associated survival advantage that would offset increased high grade toxicity. A study comparing intravenous topotecan and CAV chemotherapy showed that the topotecan group had higher risks of anemia and thrombocytopenia. High-dose platinum/etoposide had more leukopenia than low-dose platinum/etoposide.

Five multicenter phase II trials of note published since 2000 have reported overall response rates of 20% or more. Only one study, using topotecan plus cisplatin, enrolled more than 50 patients. Approximately one fourth of both sensitive and refractory patients responded. Three-quarters or more of both patient groups had high grade leukopenia and neutropenia. A small study of irinotecan plus cisplatin found very high rates of partial response and low hematologic toxicity. The combination of paclitaxel, ifosfamide and cisplatin achieved a high ORR and high grade leukopenia in nearly all patients. One-quarter of those given paclitaxel plus carboplatin had a response and about half had high grade neutropenia. In a study of doxorubicin plus carboplatin, nearly half of patients responded; however, 4 out of 5 had grade 3 or 4 granulocytopenia. The clinical applicability of these regimens awaits the results of randomized trials.

Chapter 5. Discussion and Future Research

The majority of evidence reviewed for this report addresses treatments added to primary chemotherapy for small cell lung cancer (SCLC). The main objective is to improve survival by increasing the rate and durability of complete response (CR) resulting from primary treatment; and, for those who do not achieve CR, to delay progression. Questions focus on whether outcomes can be optimized by manipulating variables of adjunctive treatments and their combination.

The strongest evidence available for this report shows that prophylactic cranial irradiation (PCI) improves survival of SCLC patients who achieved CR following primary therapy. Although the benefit is modest, an absolute increase of 5.4 percent in 3-year survival, the evidence is robust and convincing. For this knowledge, clinicians and their patients are the beneficiaries of the PCI Overview Cochrane Collaborative Group, which conducted an individual patient-level meta-analysis, a laborious undertaking. Thus seven discrete randomized, controlled trials were transformed into a rich source of data on almost one-thousand patients, adequate to support clinically relevant subgroup analyses. The results are encouraging in that it appears that all subgroups of eligible patients can potentially benefit from PCI, regardless of age, disease stage, performance status at diagnosis, and whether or not thoracic radiotherapy (TRTx) is part of the induction regimen. Two trials comparing alternative doses and schedules for PCI are in progress, one in the U.S. (RTOG-0212) and one in Europe (FRE-IGR-PCI-99). Targeted accrual for the two trials together is over 900 patients. These trials will provide additional data on neurotoxicity and quality of life.

Patient level meta-analysis was not available for any other key question considered in this evidence report. No other question yielded a body of evidence so robust. Where we attempted to draw conclusions, we typically relied on a single trial showing treatment effects that were modest at best, and sometimes equivocal. This was apparent in our review of evidence for the sequence, timing, dosing and fractionation of TRTx. For some questions (i.e., management of mixed-histology disease; surgery for early limited SCLC) comparative trials were nonexistent.

Perhaps the most vexing questions are those regarding the delivery of TRTx. Strategies for sequencing, timing, dosing, and fractionation are not well supported by a strong evidence base; each rests largely on a single study that shows significant findings. The case for concurrent over sequential delivery rests largely on a single multi-center trial (Takada 2002) supplemented by a smaller study judged to be of poor quality (Park 1996). We found the results to be suggestive, but not conclusive, of better outcomes for concurrent over sequential TRTx. No studies show an advantage for alternating TRTx, but none show it to be inferior. Support for early concurrent therapy comes largely from the results of the multicenter trial by Murray-Coy-Feld (Murray, Coy, Pater, et al., 1993/Coy, Hodson, Murray, et al., 1994/Feld, Payne, Hodson, et al., 1988); but two other multicenter trials, one using non-platinum chemotherapy (Perry, Eaton, Propert, et al., 1987/Ahles, Silberfarb, Rundle, et al., 1994/Perry, Herndon, Eaton, et al., 1988) and the other not yet published in full text (James, Spiro, O'Donnell, et al., 2003), found no advantage. We conducted a meta-analysis of 11 studies, which did not find significant reductions in 2- and 3-year mortality for early TRTx over late TRTx.

Compared to a single daily fraction, two fractions per day of accelerated TRTx delivered concurrently with platinum chemotherapy improved overall survival in a large multicenter trial of good quality (Turrisi, Kim, Blum, et al., 1999/Yuen, Zou, Turrisi, et al., 2000). In contrast to

a subsequent study comparing single to twice-daily fractionation (Schild, Bonner, Shanahan, et al., 2004/Sloan, Bonner, Hillman, et al., 2002/Bonner, Sloan, Shanahan, et al., 1999), which is difficult to interpret because multiple variables were studied simultaneously, the Turrisi study compared only the variable of fractionation. An approach to comparing early- versus late-concurrent TRTx, would be to reproduce this twice daily fractionation regimen varying only the element of timing. In concept, late-concurrent TRTx could be advantageous if better tolerated, thus permitting more patients to complete their full course and intensity of chemotherapy. In contrast, our meta-analytic sensitivity analysis suggests that an advantage for early TRTx depends on use of hyperfractionation, a finding that is hypothesis-generating only.

With respect to treatment for extensive-stage disease, results reported by Jeremic, Shibamoto, Nikolic et al. (1999) on the addition of TRTx to chemotherapy need replication in a multicenter setting. This applies both to the evidence suggesting benefit from TRTx for those with complete disappearance of extrathoracic lesions after three cycles of platinum/etoposide, and to the uncontrolled evidence suggesting little or no benefit if extra-thoracic lesions only partially respond.

Use of positron emission tomography (PET) as an adjunct to conventional tests is relevant to initial staging and restaging after treatment. Because PET may be more sensitive in detecting disease outside the brain than conventional staging modalities, and has been suggested to correctly upstage or downstage disease, it should be investigated in better quality studies to confirm these results and determine if it improves clinical management of SCLC. Currently available studies are limited primarily by inadequate quality, especially failure to define an adequate reference standard. An informative design would compare the frequency of correct upstaging, correct downstaging, incorrect overstaging and incorrect understaging for PET plus conventional staging tests in relation to conventional staging tests alone. The use of PET/CT is becoming more common and should be addressed in future studies. Future studies should be conducted according to standards described by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and reported according to the Standards for Reporting of Diagnostic Accuracy (STARD) statement.

Authors of a systematic review will rarely be proven wrong in calling for more rigorous evidence from well-conducted, randomized, controlled trials. However, it is also fair to acknowledge that some diseases and treatments pose greater difficulties in conducting trials to evaluate the effectiveness of interventions. A central challenge in evaluating treatments for SCLC is that overall disease outcome is poor and, at this time, the potential for an intervention to change the course of disease is limited. Because treatment effect sizes are small, large numbers of patients are needed in trials to test effectiveness. Complicating this is the multimodal nature of interventions and, as exemplified by TRTx, the multiplicity of variables that might contribute to the effectiveness of a single component of a multimodal intervention. And for some populations of interest (i.e., mixed histology disease; early limited disease), the number of affected individuals is small, making prospective study difficult.

The very circumstances that comprise the challenges to research in SCLC highlight the necessity of setting a systematic and rigorous research agenda to accumulate findings that can improve clinical care and outcomes. To this end, we make the following recommendations for future research.

- In assessing strategies for the delivery of multimodality interventions, such as TRTx, design trials to clearly test a single variable (e.g., early concurrent vs. late concurrent). Multi-arm trials could permit testing of more than one variable simultaneously. Given

the potential complexity of variables and combinations, there should be a consensus on the priority of strategies and elements to be tested.

- Trials that are poorly designed, conducted, or reported waste limited resources. To advance clinical knowledge and practice, the field should adhere to standards of research quality, as well as setting an agenda for research priorities.

- Quality of life assessment should be an integral to clinical trials. Given modest gains in survival, it is important to assess the quality of the survival. Quality of life research poses intrinsic difficulties, including missing data as disease progresses. Studies should adhere to recommended methods for quality of life research and handling of missing data.

- Future trials should use consensus definitions for patient enrollment criteria, subgroup characteristics and trial endpoints. Adverse events data should be consistently reported and collected. The use of consistent definitions and end-points can produce a more robust body of cumulative evidence improving the ability to compare results among trials and increasing the potential for combined analyses.

Finally, clinicians and investigators would be well-served by improved indexing and search terms so that electronic literature databases would better distinguish records on SCLC from those on non-small cell lung cancer.

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List of Acronyms/Abbreviations

-	without
#	number
#	number
∆	change
?	unknown, unclear
+	with
<p	less than a partial resection
1°	primary
18-FDG	18-fluorodeoxyglucose
95% CIL	lower limit 95% confidence interval
95% CIU	upper limit 95% confidence interval
A	Asian
A	doxorubicin (Adriamycin®)
abstr	abstract
ACCP	American College of Chest Physicians
AHRQ	Agency for Healthcare Research and Quality
ALT	alanine transaminase
Alt	alternating
AP	anterioposterior
ASCO	American Society of Clinical Oncology
AST	aspartate transaminases
ASTRO	American Society for Therapeutic Radiology and Oncology
B	bilobectomy
B	Black
BSC	best supportive care
c	complete
C	cyclophosphamide
CALGB	Cancer and Leukemia Group B
Cb	carboplatin
CCNU	lomustine
CD	cyclophosphamide- and/or doxorubicin-based chemotherapy
chemoTx	chemotherapy
CI	confidence interval
CNS	central nervous system
Conc	concurrent
cont'd	continued
contr	contralateral
Conv	conventional
CPHM	Cox proportional hazard model
CR	complete response
CT	computed tomography
Ctrl	control
CTx	chemotherapy
d	day
DA	diagnostic accuracy
dist	distant
Dx	diagnosis
E Alt	early alternating
E	etoposide
E	etoposide
ea	each
ECOG	Eastern Cooperative Oncology Group
endosc	endoscopic
EORTC LCCG	European Organization for the Research and

	Treatment of Cancer Lung Cancer Cooperative Group
EPC	Evidence-based Practice Center
EQ-5D	EuroQOL 5-dimension health-related quality of life instrument
ES	extensive stage
ESD	extensive-stage disease
F	female
F	fractions
F/d	fractions per day
F/U	follow-up
FDA	Food and Drug Administration
FE	fixed effects
FEV1	forced expiratory volume in 1 second
FN	false negative
FNA	fine-needle aspiration
FP	false positive
Frac(s)	fraction(s)
FWHM	full width, half maximum
GQ	good quality
Gy	Gray
H	Hispanic
HL	hilar
HR	hazard ratio
hr	hour
Hyper	hyperfractionated
ips	ipsilateral
IV	intravenous
K-M	Kaplan-Meier
KPS	Karnofsky Performance Status
L Alt	late alternating
L	lobectomy
L	lomustine
L95	upper limit 95% confidence interval
LCSG	Lung Cancer Study Group
LDH	lactic dehydrogenase
LINAC	linear accelerator
LN	lymph node
LRFS	local recurrence-free survival
LRFS	local recurrence-free survival
LS	limited stage
LSD	limited-stage disease
M	male
M	methotrexate
MBq	megabecquerel
mCi	milliCurie
md	median
MD	mediastinal
mets	metastases
MeV	megaelectron volt
mg	milligram
M-H	Mantel-Haenszel
MI	myocardial infarction
mn	mean
mo(s).	month(s)
MR	meta regression
MRI	magnetic resonance imaging
MS	mediastinal
N	no
n	number
N	pooled number
NCI	National Cancer Institute

NE	not evaluable
NED	no evidence of disease
neg	negative
NNEC	non-neuroendocrine carcinoma
NNT	number needed to treat
nonrandom.	nonrandomized
NOS	not otherwise specified
NR	not reported
NS	nonsignificant
NSCLC	non-small-cell lung cancer
O	other
OR	odds ratio
ORR	overall response rate
OS	overall survival
P	cisplatin
p	partial
P	pneumonectomy
PA	posterioanterior
PCI	prophylactic cranial radiation
PD	progressive disease
PE	platinum/etoposide chemotherapy
PET	positron emission tomography
PFS	progression-free survival
PI	primary investigator
po	oral
P-OR	Peto odds ratio
pos	positive
PR	partial response
PS	performance status
Pt	platinum
pub	publication
PWIFR	percent/proportion with in-field recurrence
Q	heterogeneity statistic
QoL	quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
R/I	ruled in
R/O	ruled out
radiol	radiologic
RadioTx	radiotherapy
RCT	randomized, controlled trial
RD	risk difference
RE	random effects
reg	regimen
regl	regional
retrospect	retrospective
RFS	recurrence-free survival
rng	range
RNS	radionuclide scan
ROC	receiver operating characteristic
RR	relative risk
RR	risk ratio
SC	supraclavicular
SC/LC	small-cell/large-cell subtype
SCLC	small cell lung cancer
SD	stable disease
SE	standard error
Sens	sensitivity
Seq	sequential
Spec	specificity
STARD	Standards for Reporting of Diagnostic Accuracy
sup-clav	supraclavicular
supraclav	supraclavicular

surg	surgery
SWOG	Southwest Oncology Group
T	thoracotomy only (open and close)
TN	true negative
TNM	Tumor, Node, Metastasis (staging system)
TP	true positive
TRTx	thoracic radiotherapy
TTF	time to failure
Tx	treatment; therapy
U.S.	United States
U95	upper limit 95% confidence interval
ULN	upper limit of normal
US	ultrasound
V	vincristine
VC	vital capacity
Ve	vindesine
W	White
WBC	white blood cell
WHO	World Health Organization
wk(s)	week(s)
Wt	weight
XRT	radiotherapy
Y	yes
yr	year

Abbreviations of Combination Chemotherapy Regimens

ACO	doxorubicin, cyclophosphamide, and vincristine
ACOM	doxorubicin, lomustine, methotrexate, vincristine
BTOC	vincristine, thiotepa, cyclophosphamide, carmustine
CAE	cyclophosphamide, doxorubicin, etoposide
CAV	cyclophosphamide, doxorubicin, vincristine
CbE	carboplatin, etoposide
CbPE	carboplatin, cisplatin, etoposide
CC	cyclophosphamide, lomustine
CCM	cyclophosphamide, lomustine, methotrexate
CCMV	cyclophosphamide, lomustine, methotrexate, vincristine
CDE	cyclophosphamide, doxorubicin, etoposide
CE-CAP	cyclophosphamide, doxorubicin, cisplatin
COME	cyclophosphamide, vincristine, methotrexate, etoposide
COMF	cyclophosphamide, vincristine, methotrexate, fluorouracil
CVMP	cyclophosphamide, vincristine, methotrexate, cisplatin
EP	etoposide, platinum compound
LCAE	lomustine, cyclophosphamide, doxorubicin, etoposide
M-CAV	methotrexate, cyclophosphamide, doxorubicin, vincristine
MCCC/VI	methotrexate, cyclophosphamide, lomustine, ifosfamide, etoposide
PE	cisplatin, etoposide
PEVe	platinum, epirubicin, etoposide
PMP	cisplatin, methotrexate, procarbazine
VCMV	vincristine, cyclophosphamide, mitomycin, chromomycin
VIC-E/VICE	vincristine, ifosfamide, carboplatin, etoposide
VIMP	vincristine, ifosfamide, mesna, carboplatin
VIP-E	etoposide, ifosfamide, cisplatin, and epirubicin